James A Kleeman

PROGRAM OF ANNUAL MEETING, MAY 19, 20, 21 and 22, HOTEL STATLER, BOSTON

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The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Volume 236 MAY 8, 1947 Number 19

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Owned and Published by the Massachusetts Medical Society

Published weekly at 8 Fenway, Boston 15, Massachusetts.
Domestic, $6 per year, 25c per copy (medical students, $3.50 per year); Canada, $7.00 (Boston funds); foreign, $8.50.
Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.
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Paid Circulation 22,841

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The New England
Journal of Medicine

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Volume 236 MAY 8, 1947 Number 19

BENIGN AND MALIGNANT TUMORS OF THE SMALL INTESTINE*

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BOSTON

THE small intestine comprises the longest portion of the alimentary canal and yet receives small consideration in the diagnosis of intestinal tumors. The reason is the rarity of neoplasms in the small bowel. Such easy setting aside is in line with the attitude toward these tumors in general and can no longer be tolerated by the profession. Moreover, tumors of the small intestine are possibly curable in the early stages, and certainly the small bowel is heir to a variety of benign tumors that may cause symptoms. The diagnosis of the lesions is usually obscure, and until the physician entertains the possibility, it will remain obscure.

It is the purpose of this communication to stress factors that may aid in the early diagnosis of small-bowel tumors and to review the primary cases seen at the Peter Bent Brigham Hospital. X-ray diagnosis of these tumors is especially emphasized. The material for this report was obtained from the clinical and autopsy records of the hospital from 1913 to 1946. Only histologically verified benign and malignant primary tumors of the duodenum, jejunum and ileum are included. Carcinomas of the head of the pancreas and of the ampulla of Vater are not considered. Several cases in the present series have previously been reported. Oughterson and Cheever[1] and Botsford and Newton[2] each reported a case of submucous lipoma of the ileum, and Newton and Buckley[3] reported one of carcinoma of the jejunum. In 1934 Bailey[4] included 8 instances of argentaffinoma of the jejunum and ileum in his exhaustive study.

A total of 65 cases of primary small-bowel tumor were found, and in 33 of these the tumors were malignant. Shallow, Eger and Carty[5] state that primary cancer of the small intestine occurs in 0.1 per cent of all cases in which autopsies are performed and is thirty-six times less frequent than malignant tumors of the colon, but that 60 per cent of intestinal sarcomas are located in the small bowel. Horsley,[6] however, was able to collect 243 cases of carcinoma of the jejunum and ileum from the literature between 1932 and 1941; it is of interest that in 7 cases the lesions were primary in a Meckel's diverticulum. Benign tumors of the small bowel are also rare, but are probably more frequent than is realized, since they seldom cause symptoms.

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TYPES OF TUMOR

The types and location of the tumors are presented in Table 1. Adenocarcinoma was the most frequent tumor, occurring about equally throughout the small intestine, although the percentage localization based on length of bowel indicated a greater incidence in the upper part of the small intestine. Argentaffinoma constituted the next most frequent group, but these tumors were invasive in only 2 cases. Lymphosarcoma, next to adenocarcinoma, was the largest malignant group of clinical significance. The benign tumors — submucous lipoma, adenoma, leiomyoma and fibroma — comprised about a fourth of the whole series and were the cause of symptoms in only 3 cases. Rankin and Newell[7] reported a higher incidence of symptoms due to benign lesions but did not include argentaffinomas in their series. In 32 cases in our series, in all of which the tumors were benign except for 1 case with a locally invasive argentaffin tumor and 2 with small carcinomas of the duodenum, the lesions were incidental findings at autopsy. A careful review of the corresponding clinical records showed no evidence of their having caused symptoms. Raiford[8] reported 60 per cent benign lesions and 40 per cent malignant tumors in his series and pointed out that 49 per cent were incidental findings. In our series, the ileum, where lymphosarcomas and argentaffinomas characteristically occur, was the most frequent portion of the small intestine involved. There were 38 men and 27 women. The maximum incidence was in the sixth and seventh decades, but in 10 cases the malignant tumors occurred in pa-

tients between thirty-five and forty-five years of age. It follows that the majority of small-bowel tumors that cause symptoms are malignant and that about a third of these are seen in patients under fifty years of age.

Carcinoma

Adenocarcinoma is the usual type encountered,[9] and in our series all the lesions in this group were adenocarcinomas. One tumor of the duodenum arose in an ulcer, and another in the same location arose in an adenomatous polyp. Metastasis to the regional lymph nodes, which occurs early, was grossly present in all but 2 cases at the time of operation or autopsy. It is of special interest that duodenal adenocarcinomas were incidental findings in 2 patients with carcinoma elsewhere in the gastrointestinal tract. The stomach was involved in one patient, and the sigmoid in the other, those lesions being the cause of the symptomatology and the reasons for hospitalization. The typical adenocarcinoma of the small bowel gives an annular constriction to the intestine and is not a large tumor (Fig. 1). Distant metastases are frequent late in the course of the disease.

Lymphosarcoma

Lymphosarcoma, which originates in the lymphoid tissue of the bowel wall, generally occurs in the ileum, and the mesenteric lymph nodes are involved early. The lesion is usually diffusely infiltrating and not confined to a small area of the intestine (Fig. 2). Because of this, a mass is frequently palpated; in 11 of our patients with lymphosarcoma there was a palpable mass, whereas in only 2 patients with adenocarcinoma was such a mass present. It is of more than academic interest to repeat that most of these tumors were seen in the fourth decade of life.

In this study, lymphosarcoma of origin in the bowel wall was carefully separated from lymphosarcoma or lymphoma originating in the mesenteric lymph nodes. The latter rarely invades the bowel wall, although intestinal symptoms may arise from mechanical causes.

Argentaffinoma

Argentaffin tumors, or carcinoids, arise from the Kultschitzky cells in the depths of the mucosal glands. They are characteristically located in the vermiform appendix and less frequently in the terminal ileum, but are occasionally seen in the stomach, jejunum and cecum. They are usually regarded as benign tumors, but occasionally they become malignant, with local invasion and distant metastases. They grow slowly in contradistinction to lymphosarcoma and carcinoma, and radical resection is indicated even in the presence of distant metastases. Four patients had from two to nine multiple tumors. The usual carcinoid is seen at autopsy as a small nodule with a distinctive yellowish color.

There were two malignant carcinoids in our series, both of which have been described by Bailey.[4] One was found to be invading the mesentery of a patient who had died of an unrelated cerebral tumor. The other, which was the cause of intestinal obstruction, had encircled only part of the circumference of the ileum but had spread to the adjacent mesentery and to the liver. Radical resection of the local lesion was performed. The patient died six years after recognition, and autopsy showed a small local recurrence and extensive liver involvement.

Lipoma

Lipomas of the small intestine are benign fatty tumors located in the submucosa and are usually pedunculated (Fig. 3). Their importance clinically lies in the fact that they may initiate an intussusception. This occurred in 3 of our 9 cases. Two of these patients, who were successfully treated and are living and well, have been reported.[1,2] The third patient had multiple submucous lipomas with intussusception, but the disease was not recognized ante mortem, although it was the cause of death.

Adenoma

Adenomas of the small bowel are small pedunculated tumors that may undergo malignant changes

TABLE 1. *Types of Tumor in 65 Cases.*

LESION	LOCATION			CAUSE OF SYMPTOMS	INCIDENTAL FINDING
	DUODENUM	JEJUNUM	ILEUM		
Adenocarcinoma	6	7	5	16	2
Argentaffinoma	0	1	15	1	15
Lymphosarcoma	0	1	12	13	0
Submucous lipoma	1	1	7	3	6
Adenoma	3	2	0	0	5
Leiomyoma	0	1	1	0	2
Fibroma	0	1	1	0	2
Totals	10	14	41	33	32

or initiate intussusception. None of the tumors in the 5 cases in this series were the cause of any difficulty. One carcinoma of the duodenum arose in an adenoma.

Fibroma

Two cases of small pedunculated fibroma of the small bowel were encountered as incidental findings. They may cause the same difficulties as leiomyomas.

FIGURE 1. *Adenocarcinoma of the Jejunum.*

The photograph of the gross specimen shows a typical annular tumor. Note the dilated proximal portion of the intestine. This tumor was not palpable preoperatively. With the lumen of the bowel opened, the small size of the tumor is more apparent.

Leiomyoma

There were only two leiomyomas, both of which were incidentally found as sessile tumors measuring a few millimeters in diameter. The lesions rarely cause intussusception or undergo sarcomatous degeneration.

SYMPTOMATOLOGY

All observers are agreed that no characteristic clinical picture is associated with benign or malignant tumors of the small intestine. The symptoms due to these lesions, however, are those either of obstruction or of bleeding into the alimentary canal with the development of secondary anemia. The

benign tumors can be the source of considerable blood loss,[7] although there was no bleeding in our series. Intussusception, initiated by a benign tumor, is occasionally seen and is the usual way that such tumors cause intestinal obstruction. Intussusception was caused by benign lesions in 3 cases, all of which had submucous lipomas. Otherwise, the benign tumors caused no symptoms. Rankin and Newell[7] reported 35 cases of benign tumors of the small bowel, in 18 of which the lesion caused hemorrhage or intestinal obstruction.

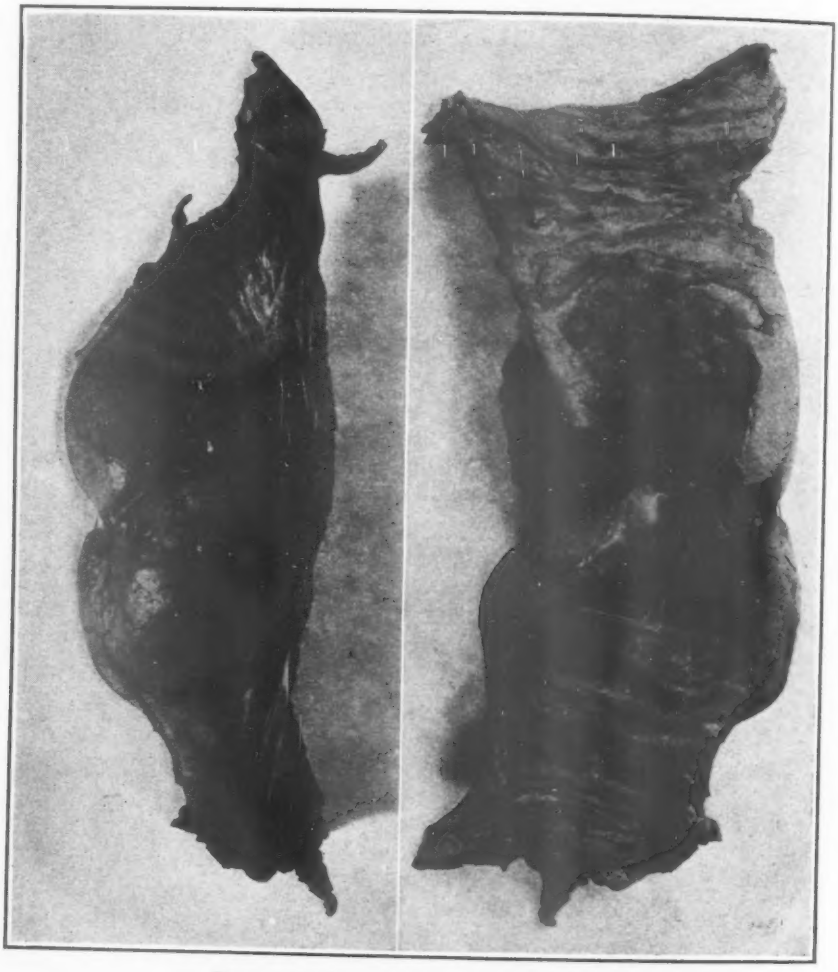

FIGURE 2. *Lymphosarcoma of the Ileum.*

As shown by the photograph of the gross specimen, this lesion is larger and more diffuse than that of the carcinoma shown in Figure 1. The tumor was easily palpable preoperatively. The extent of the lesion is more apparent in the photograph taken after the lumen had been opened.

The symptoms caused by malignant lesions in 30 cases are summarized in Table 2. The duration varied from a week to two years, with an average of about four months for lymphosarcoma and five months for adenocarcinoma. The patient with malignant argentaffinoma had had symptoms for two years. Adenocarcinoma differed clinically from lymphosarcoma in that abdominal pain was rare and that 3 patients with carcinoma complained only of the symptoms of secondary anemia. Newton and Buckley[3] pointed out that anatomically identical adenocarcinomas of the small bowel can present the picture of intestinal obstruction or can only show symptoms of secondary anemia without any gastrointestinal symptoms, although the lesion may be high in the jejunum. It is of further interest that a palpable abdominal mass was observed in only 2 patients with carcinoma. Intussusception may be initiated by adenocarcinoma[9,10] but was not present in our series. Another important point in the history of patients with small-bowel carcinoma is that many have had barium roentgenologic studies of the stomach and colon, not once but several times, with negative findings and have therefore occasionally been told that they have a "nerv-

ous stomach." Although it is obvious that the clinical picture may be obscure, patients with symptoms of chronic intermittent intestinal obstruction or of secondary anemia of gastrointestinal

X-Ray Diagnosis

The accurate early diagnosis of tumors of the small intestine ultimately depends on careful roentgenologic barium-contrast studies. It is our

Table 2. *Symptoms in 30 Cases of Malignant Small-Bowel Tumor.*

Lesion	Location	Vomiting	Constipation	Abdominal Pain	Gross Melena	Secondary Anemia	Palpable Abdominal Mass
Adenocarcinoma (16 cases)	Duodenum	4	4	1	—	—	—
	Jejunum	5	5	—	—	2	1
	Ileum	4	4	—	—	1	1
Lymphosarcoma (13 cases)	Jejunum	1	1	1	—	—	1
	Ileum	6	6	10	3	—	10
Argentaffinoma (1 case)	Ileum	1	1	1	—	—	1

origin must have roentgenologic investigation of the small intestine if an adequate explanation is not found in the stomach or colon.

Lymphosarcoma, in our experience, presented a more clear-cut picture, in that an abdominal mass was palpable in all except 2 patients. Abdominal pain of a crampy nature was also much more frequent, and there was usually no question that these patients had a serious abdominal disease. One patient had an ileocolic intussusception. In addition to the symptoms listed, all the patients with malignant tumors showed evidence of weight loss.

opinion that any patient with signs or symptoms referable to alimentary-tract obstruction or bleeding should have x-ray investigation of the small intestine, provided a satisfactory explanation for the clinical picture is not found in the esophagus, stomach or large intestine. In this respect it is well to remember that a peptic ulcer may coexist with a jejunal or ileal tumor.

Figure 3. *Submucous Lipoma of the Ileum.*

The tumor was the leading point of an ileocolic intussusception. The diagnosis was made by barium enema.

Methods of Examination

Unless there is definite evidence of small-bowel obstruction, the course of the x-ray investigation

should first rule out lesions in the colon, stomach and duodenum by the usual methods of x-ray examination — that is, the barium enema and gastrointestinal series. These examinations not only serve to exclude lesions in the colon, stomach and duodenum but also may give the first clue of the presence of a neoplasm in the jejunum or ileum. For example, the barium enema may disclose the presence of intussusception of the ileum into the colon on the basis of a tumor of the terminal ileum. This point is discussed in more detail below.

X-ray examination may also disclose segments of small intestine filled with air, fluid or barium that, in view of the symptoms, should immediately arouse suspicion of a tumor and lead to further investigation. At this hospital, the routine gastrointestinal series includes the giving of a barium motor meal six hours before the fluoroscopic examination. If, at the time of fluoroscopy, the barium meal demonstrates a dilated segment of jejunum or ileum or shows almost complete retention of the barium in the stomach, with no demonstrable point of obstruction proximal to the ligament of Treitz, obstruction beyond this point should be sought.

Occasionally, unrelated x-ray examinations give the first indication of a small-bowel lesion. In 1 case cholecystograms revealed several dilated, fluid-filled loops of small intestine faintly outlined by unabsorbed Priodax retained in the loops. Follow-up barium studies disclosed a jejunal tumor. The valuable role of plain films of the abdomen in disclosing distended air-filled intestinal loops indicating ileus or obstruction is well known and needs no further mention.[11, 12]

If, in the presence of intestinal symptoms, the gastrointestinal series and barium enema disclose no disease, more intensive study of the small intestine by special technics is indicated. In general, there are three methods available to the roentgenologist.

Motility series. This procedure is employed at various clinics under different designations and with minor variations in details of technic. The method used at this hospital is as follows. Thirty grams of barium sulfate in water is given at 8 o'clock on the morning of the examination, all food and fluids having been withheld from the patient since the previous evening. Half an hour after the ingestion of the barium, a film is taken, and this is repeated at intervals of half an hour to an hour. Each film is inspected by the roentgenologist immediately after processing, and if any abnormal segments of intestine are seen, the patient is fluoroscoped and spot films are taken as indicated. The examination is completed after the head of the barium column has reached the cecum and the terminal ileum has been well visualized. In this way the progress of the barium through the entire jejunum and ileum can be followed.

Small-bowel enema. An alternative method of examination is the small-bowel enema, as described by Schatzki.[13] This procedure consists of the passage of a Levine or Miller–Abbott tube into the duodenum so that its tip lies in the second portion. Under fluoroscopic observation, the entire small intestine is filled with a barium suspension that is allowed to run in through the tube in a slow uninterrupted flow. Spot films are taken during the examination as indicated.

The two methods outlined above may be used even in the presence of a partially obstructing lesion without danger of completing the obstruction, since the fluid state of the barium suspension is preserved in the ileum and jejunum and since there is no dehydrating action. Golden[11] states that no evidence of damage was observed after the administration of barium by mouth in the presence of disease of the small intestine, even with narrow constrictions. One of our patients offered excellent proof of this opinion. The operative specimen showed a markedly constricting carcinoma of the jejunum through which air could be forced only with difficulty, and yet a few days prior to operation, barium administered by mouth passed readily through this area to the cecum with only slight delay proximal to it and with no evidence of a deleterious effect or barium plug at operation.

If complete intestinal obstruction with ileus is present, the two methods described above should not be used because the amount of barium suspension necessary for the examination further distends already dilated loops and is difficult to withdraw through a tube with a narrow lumen. Furthermore, the procedures do not yield satisfactory results because the overlapping dilated barium-filled loops of intestine obscure the lesion, the barium is diluted greatly in the obstructed loops, and motility is absent or diminished, causing stasis of the barium proximal to the lesion. If it is desired to demonstrate the cause of an obstruction, the following method may be used.

Modified small-bowel enema. A Miller–Abbott tube is passed into the intestine, usually as a therapeutic measure when the patient is first seen. After the tube has reached the point of maximum progress and the dilated loops have been decompressed by suction, a small amount of thin barium suspension (35 to 40 cc.) is introduced through the tube just proximal to the obstruction, and under fluoroscopic observation the area of obstruction examined.[14] In this way much valuable information may be gained, and frequently the exact nature of the lesion demonstrated.

Benign Tumors

Theoretically, benign tumors should be demonstrable by x-ray examination as polypoid or smooth, round filling defects in the lumen of the intestine. Such findings are not too infrequent in the duodenum, and illustrations are readily found in the radiologic literature.[15–17] On the other hand, it is exceedingly rare to demonstrate benign tumors per se in the jejunum or ileum. Golden[11] states that he has never been able to demonstrate a benign neoplasm in this way. A review of the literature shows only one report of such findings, in which the authors describe 3 cases.[18] This infrequency is probably due to segmentation and overlapping of intestinal loops obscuring the lesions because of their small size and to the fact that the tumors rarely give rise to symptoms leading to x-ray investigation until they have caused intussusception.

The demonstration of this associated intussusception is the most frequent x-ray finding in benign tumors of the small intestine. If the tumor occurs in the terminal ileum and causes intussusception of the ileum into the cecum, the lesion can be demonstrated by barium enema (Fig. 4). If there is intussusception of one loop of small intestine into another, this may be demonstrated by oral barium. Since the filling is from the proximal side, the x-ray picture is that of a narrow, barium-filled tract lying within a loop of small intestine. If some of the barium passes distally, a thin layer may outline the intussusceptum lying within the lumen of the bowel. The loops proximal to the point of obstruction usually show dilatation.

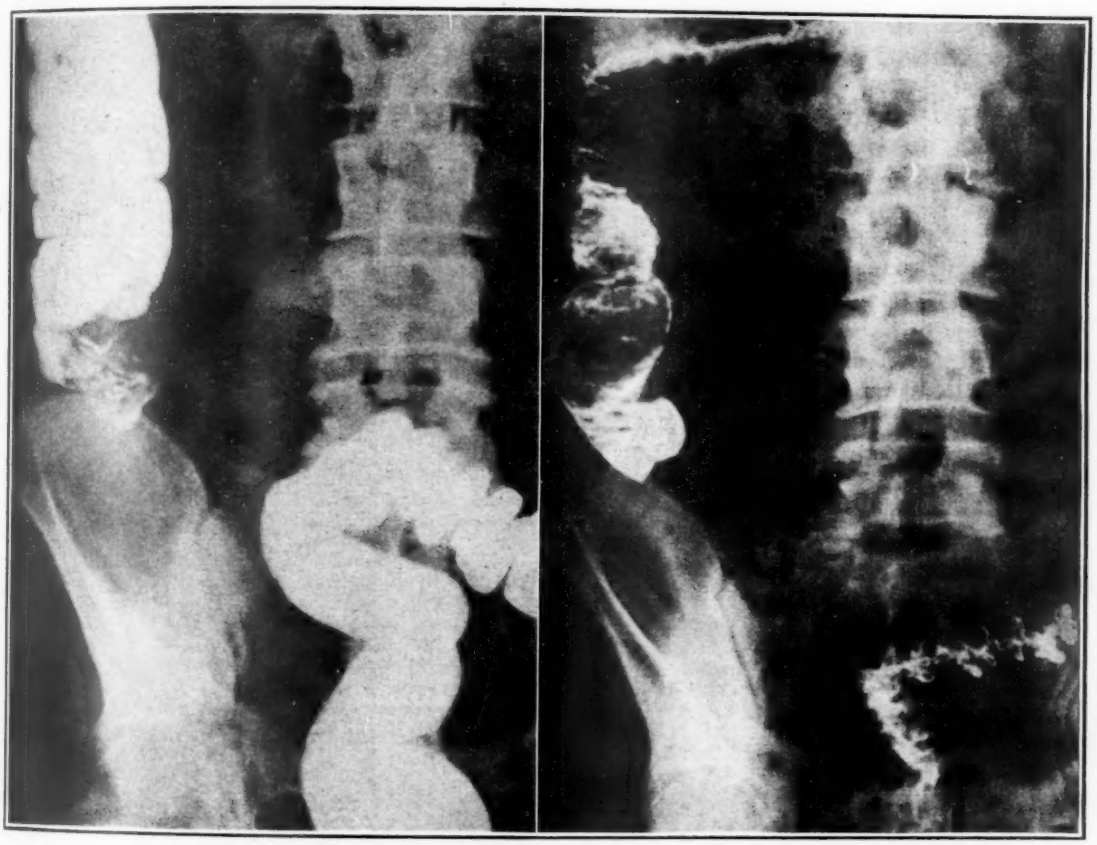

FIGURE 4. *Intussusception of the Ileum into the Cecum Caused by a Lipoma of the Ileum.*

The film on the left, taken before evacuation, shows the filling defect in the cecum made by the invaginated ileum. The film on the right, taken after evacuation, shows the valvulae conniventes of the terminal ileum as cross striations within the lumen of the cecum and lower ascending colon.

Malignant Tumors

Carcinoma. The x-ray findings in carcinoma of the small intestine vary with the type of tumor growth. The usual finding is an annular constriction with concave, shelf-like margins. Roentgenology frequently demonstrates only the proximal margin with a narrow rigid tract of barium, representing the constricted lumen through the tumor, extending from it. Occasionally, both the proximal

and the distal concave margins with a constricted area between them may be shown, giving the typical napkin-ring appearance seen in annular carcinomas of the colon (Fig. 5). The involved area is usually short, being less than 5 cm. in length, rigid and often fixed. The mucosal pattern through it is destroyed. The lesion is more circumscribed in carcinoma than ulceration within the tumor. The involved area is much longer than that seen with the annular type, all the reported lesions measuring several centimeters in length and the longest measuring 14 cm.

Frequently, the roentgenologist is able to demonstrate only the point of obstruction with dilated loops proximal to it; his interpretation must then be

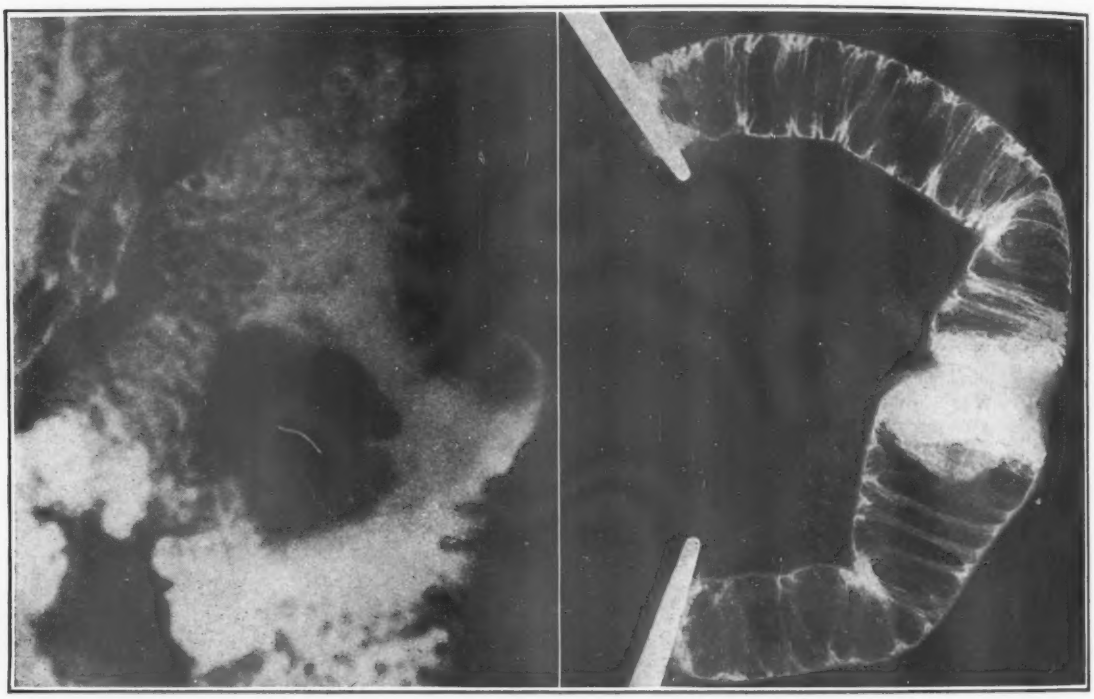

FIGURE 5. *Adenocarcinoma of the Jejunum.*

The roentgenogram on the left, an area of the plain film made during fluoroscopy, shows the constricting lesion with the characteristic biconcave shelf formation at either end. The roentgenogram on the right is of the specimen removed at operation, which was clamped at both ends and filled with air. It is apparent that the annular constricting lesion almost completely obliterated the lumen. This is the case illustrated in Figure 1.

in lymphosarcoma. Proximal to the lesion the intestine is frequently dilated and may show accordion-like pleating of the valvulae conniventes of the portion just adjacent to the tumor (Fig. 6). This is the probable result of contractile shortening of the longitudinal muscles of the intestinal wall in an attempt to overcome the obstruction. Intraluminal proliferative polypoid carcinomas are rarer and show on x-ray examination an irregular filling defect projecting into the lumen. Golden[11] reports an infiltrating type of carcinoma of the terminal ileum much longer than that ordinarily seen, with irregular borders resembling an inflammatory type of lesion. The x-ray appearance of a group of carcinomas classified as nonobstructing and extraluminal has been described by Lingley.[19] These give the x-ray picture of a large, dilated, irregular, barium-filled segment of intestine associated with a palpable mass. This appearance is the result of extensive necrosis and limited to an obstructing lesion of the small intestine of undetermined nature. Malignant, as well as benign, tumors may give rise to intussusception, with x-ray findings similar to those described above under benign tumors.

Argentaffinoma. The malignant variety of this lesion may cause an annular constriction, with an x-ray appearance that is indistinguishable from an annular carcinoma. Miller and Herrmann[20] point out that the intraluminal portion of a carcinoid that has undergone malignant change is frequently not large but that there is extension into the wall of the intestine and into the mesentery, with resultant kinking or knuckling of the intestine at the site of the tumor that produces obstruction, either partial or complete. They demonstrated these x-ray findings in 3 proved cases of carcinoid and concluded that the roentgenologic demonstration of a tumor at a point of kinking and partial obstruction is a

highly suggestive sign of these tumors. Recently, we saw in consultation the x-ray studies of a patient who was found to have an argentaffinoma involving the terminal ileum. The films showed a fairly smooth narrow segment of intestine about 10 cm. in length and with the diameter of an ordinary lead pencil. It was concave, as if stretched around a soft-tissue mass. The mucosa through the segment appeared intact but was distorted, having a fine granular appearance. There were no shelflike margins at the ends of the lesion. Fluoroscopically, it was reported to be fixed and rigid. The appearance was similar to that seen with long-standing chronic cicatrizing enteritis, or with involvement of a segment of intestine in an extrinsic chronic abscess of the peritoneal cavity.

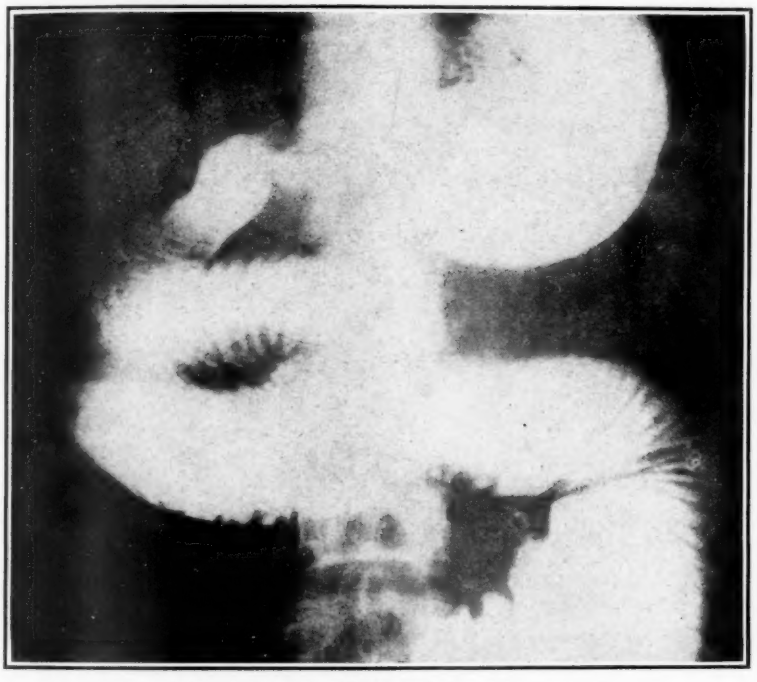

FIGURE 6. *Carcinoma of the Jejunum.*

This tumor had produced intestinal obstruction. All the barium lies in the dilated intestinal loops proximal to the lesion, which is not outlined. The roentgenogram illustrates the "closed accordion" appearance of the dilated proximal loops, with the valvulae conniventes lying closely together.

Small benign nodular submucosal carcinoids should show, theoretically, smooth dome-shaped or polypoid filling defects projecting into the lumen, frequently multiple. No reports of the demonstration of such lesions could be found in the literature or in our own records. A carcinoid as the basis of an intussusception of the ileum into the cecum was reported by Brocher.[21]

Sarcoma. Lymphosarcoma is the most frequent sarcoma involving the small intestine. This involvement may be either localized or generalized. Swenson[22] described a generalized lymphosarcomatous involvement of the small intestine in which x-ray examination showed a patchy irregular distribution of barium through the jejunum and upper ileum, with coarse irregular wall markings widely separated. Hypomobility was present. The picture resembled that seen in nutritional disturbances, such as sprue. Tannhauser and Davison[23] also described a case of the generalized form of gastrointestinal pseudoleukemia in which there were numerous polypoid growths throughout the intestine showing as multiple small intraluminal filling defects on x-ray study. The localized form may present an x-ray appearance identical with that of carcinoma. As Doub and Jones[24] state, the tumors may be divided into three groups: the annular constricting lesions, which they consider rare in sarcoma; the subserous tumors, which show ulcerated and aneurysmal dilatations of the lumen of the involved segment; and those that present a polypoid intraluminal mass. In general it may be said that lymphosarcoma tends to involve a longer segment of intestine than carcinoma and less often causes marked constriction. The involved segment shows either an irregular lumen of normal or slightly less than normal caliber or actual dilatation and widening of the lumen owing to ulceration and necrosis.

Lymphosarcoma is likelier to produce multiple lesions than carcinoma, and there is frequently an associated palpable mass. The involved area is usually more irregular than that of carcinoma.

Swenson[22] states that x-ray examination frequently shows a longer segment to be involved than on nonobstructing extraluminal malignant tumors. Lingley[19] described 3 cases in which the sarcoma presented an x-ray appearance similar to that discussed above under carcinoma. This appearance is more frequently seen with sarcoma than with carcinoma. Sarcomas, like the other malignant tumors,

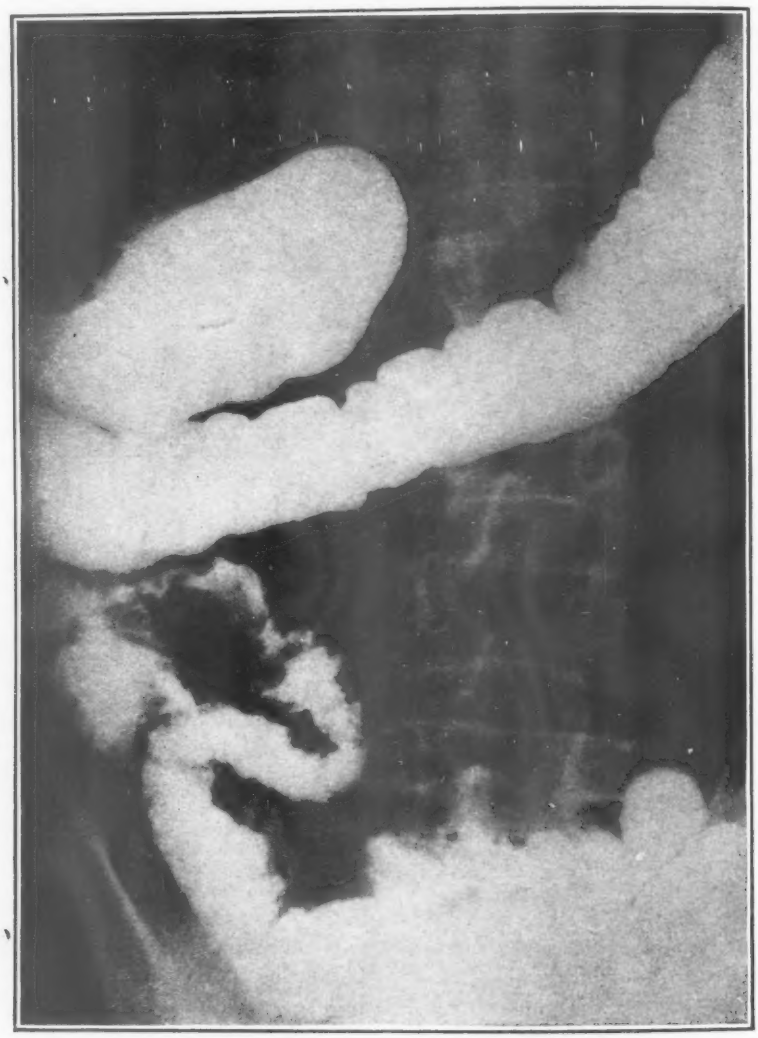

FIGURE 7. *Lymphosarcoma of the Terminal Ileum.*

This roentgenogram shows irregularity of the involved ileum, with filling defects distal to the ileocecal valve, which indicate involvement of the cecum. The mucosa is destroyed throughout the area of the lesion. The caliber of the involved bowel is normal or only slighily constricted. Lymphosarcoma produces changes closely resembling inflammatory lesions.

is actually found at operation or autopsy. He believes that this is caused by mesenteric extension of the tumor, with blocking of the lymphatic vessels and disturbance of the autonomic nervous control causing distortion of the mucosa and the lumen beyond the actual limits of the tumor. In an article may produce lesions that remarkably resemble cicatrizing enteritis on x-ray study, especially if they occur in the terminal ileum. Menne[25] reported such a case, and one of our cases presented this appearance (Fig. 7). Associated involvement of the cecum seen with sarcomas may help in the differential

diagnosis. The lesions may likewise be the basis of intussusception. This is especially true of myosarcomas.

Treatment

The treatment of choice is resection of the involved segment of bowel along with its adjacent mesentery and restoration of the continuity of the intestine. In the jejunum and ileum, resection and end-to-end or side-to-side anastomosis is performed. The duodenum, however, presents a more complicated technical problem because of its anatomic position. None of the lesions of the duodenum in our series were operable, but the logical attack on a malignant primary tumor of the duodenum is along the lines pointed out by Whipple[26] for resection of carcinoma of the head of the pancreas or the ampulla of Vater. An excellent review of the types of operative procedures in this field is given by Orr.[27] X-ray therapy was given postoperatively to all patients with lymphosarcoma. The radiosensitivity of these tumors is well known,[28, 29] but the results are usually temporary and palliative.

Table 3. *Surgical Procedures in 32 Cases of Small-Bowel Tumor.*

Lesion	Site	Resection and Anastomosis	Sidetracking Entero-enterostomy	Exploratory Laparotomy and Biopsy	Posterior Gastro-enterostomy	Cholecysto-gastrostomy	Enterostomy	Subtotal Gastric Resection (Polya)	No Surgery
Adeno-cinoma	Duodenum	5			1	1		2	2
	Jejunum	3	2	2					
	Ileum		1						
Lympho-sarcoma	Jejunum								
	Ileum	5	1	3		1			2
Argentaffi-noma	Ileum	1							
Totals		14	4	5	1	1	1	2	4

A summary of the surgical procedures in this series is given in Table 3. In only 2 patients with adenocarcinoma of the duodenum was the diagnosis apparent at the time of operation, and both lesions were inoperable. In the other 2 cases in this group carcinoma was found incidentally on microscopical examination of the specimen removed at subtotal gastrectomy for duodenal ulcer. One of these patients is living and well ten years after operation, and the other did not respond to follow-up query. The malignant tumors of the jejunum and ileum were resectable in 14 of 24 cases, and in the remainder, an exploratory operation, alone or in combination with a palliative sidetracking procedure, was done. Four patients had no operation.

The survival period for the patients with malignant tumors of the jejunum and ileum was universally short. The average survival of 22 patients who underwent operative procedures was eleven and a half months for adenocarcinoma and six months for lymphosarcoma. There was no response to follow-up query in 3 cases, but 1 patient was living and well four years after resection of the ileum for lymphosarcoma, when he was lost to follow-up. One patient* is living and well six years after resection of a carcinoma of the jejunum. A single patient with a recent case of carcinoma of the jejunum is living and well seven months postoperatively. The obvious causes for these poor therapeutic results are the facts that the diagnosis is made late and that the tumors metastasize early via the lymphatic vessels.

The 2 cases of intussusception caused by submucous lipomas of the small intestine were treated by resection and end-to-end anastomosis. Both patients are living and well five and fifteen years respectively after operation. Excellent results should be achieved in benign lesions, provided that the complicating obstruction or hemorrhage is recognized before it becomes irreversible. It should be remembered that benign lesions may be multiple, and the whole small bowel should be explored if the patient's condition warrants it.

Summary

Sixty-five cases of benign and malignant primary tumors of the duodenum, jejunum and ileum are reviewed. In 33 the tumors were malignant: 18 were adenocarcinomas, 13 were lymphosarcomas and 2 were invasive argentaffinomas.

Thirty-three patients had symptoms caused by small-bowel tumors of which 30 were malignant tumors. Only 3 benign tumors were the cause of symptoms, and in each case there was an associated intussusception.

The ileum was the most frequent portion of the intestine involved, but 13 cases of adenocarcinoma occurred in the duodenum or jejunum.

The symptoms of small-bowel tumor are those of obstruction or anemia following bleeding into the alimentary tract. No characteristic clinical picture was presented.

The diagnosis depends on thorough barium-contrast roentgenologic investigation of the small bowel in every patient with suggestive symptoms

*This is a patient of Dr. Robert Zollinger, who studied her in this hospital but performed the operation at an outside hospital. The case represents one of the longest survivals of carcinoma of the small intestine that we have been able to find.

unless a satisfactory cause is found in the stomach or colon.

The indications and methods of roentgenologic investigation are described in detail.

The treatment of choice is radical surgery, but the results of such therapy in malignant small-bowel tumors are poor.

Earlier diagnosis is the only way in which the results of treatment can be improved, and that depends on the more frequent examination by barium-contrast roentgenologic studies of the small bowel.

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VASOMOTOR DISTURBANCES IN POLIOMYELITIS, WITH SPECIAL REFERENCE TO TREATMENT WITH PARAVERTEBRAL SYMPATHETIC BLOCK

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HOT SPRINGS, ARKANSAS

POLIOMYELITIS in adults can no longer be considered unusual. Lewin[1] states that the incidence is definitely increasing in the older age groups. At the Army and Navy General Hospital, Hot Springs, Arkansas, a center for poliomyelitis patients, 131 cases in military personnel were studied. Practically all the cases were convalescent — that is, the acute symptoms had subsided and the patients were observed prior to the end of the two-year interval arbitrarily set as the convalescent period.

In a review of these cases vasomotor and sudomotor disturbances frequently appeared in the extremities. These changes formed an important part of the symptomatology and consisted of varying degrees of cyanosis or discoloration of the skin, accompanied by mild to severe edema and hyperhidrosis. The most frequent indications of vasomotor disturbances were coldness and sweating of the part involved.

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In an attempt to alleviate these distressing symptoms complicating poliomyelitis, paravertebral sympathetic blocks were performed; the results in 17 cases are reported below.

Technic

Patients scheduled for sympathetic block were premedicated with 0.2 gm. of sodium amytal ninety minutes prior to nerve block and with a small dose of morphine and scopolamine one hour prior to nerve block. Lumbar paravertebral sympathetic block was performed on patients with involvement of the lower extremities, and stellate-ganglion block on those with involvement of the upper extremities.

The technic of lumbar sympathetic block employed was essentially that of Ochsner and DeBakey.[2] Patients were placed in the lateral recumbent position; for purposes of comparison, only one side was given a course of injections at a time. The landmarks employed were the spinous processes, the transverse processes and the bodies of the lumbar vertebras. Skin wheals were raised 4 to 6 cm. lateral to the upper part of the spinous processes

of the first four lumbar vertebras. The tissues down to the transverse processes were then infiltrated with 1 per cent procaine, a 22-gauge, 7.5-cm. needle being used. Particular attention was given to the muscle fascia and the periosteum of the transverse processes, because contact with these structures was invariably uncomfortable. Next, 20-gauge, 12.5-cm. sympathetic-block needles were inserted through wheals perpendicular to the skin to make contact with the transverse processes. The needles were then withdrawn and redirected about 30° medialward and 30° cephalad, so as to pass above the transverse processes until the body of the vertebra was touched. As soon as contact with the body had been made, the needle was further introduced so as to slide off the body of the vertebra and to be near the anterolateral surface of the body. After aspiration showed the needle not to be in a blood vessel, 6 cc. of 2 per cent procaine was injected.

Stellate-ganglion block was performed by an anterolateral approach, similar to that of Volpitto.[3] The midpoint of the clavicle on the side to be injected was located, and a skin wheal raised about 2 cm. above this point. A 22-gauge, 7.5-cm. needle was inserted through the skin wheal downward medially and posteriorly to make contact with the first rib. The needle was then withdrawn and swung into the frontal plane of the body and perpendicular to the midline. In this position, the needle lay almost flush with the skin of the supraclavicular area. On further introduction the tip impinged on bone either of the transverse process of the seventh cervical vertebra or the neck of the first rib or the body of the seventh cervical vertebra between these two points. Approximately 8 cc. of 2 per cent procaine solution was then injected.

Observations

All patients treated showed definite improvement of the peripheral vascular system. Changes usually occurred within five or ten minutes after injection. Subjectively, many patients experienced a "hot foot," and stated, "I can't remember when my foot felt so good." The duration of this improved feeling following the first block was about three days. After subsequent blocks the improvement was progressively prolonged. In 8 cases after the third block there was subjective improvement for ten weeks. In Case 4 after the third block improvement lasted for four months (Table 1).

Objectively, all manifestations of vasospasm disappeared within twenty minutes after procaine injection. Color changes occurred early and were closely followed by a rise in temperature; the transition from a cold cyanotic extremity to a warm pink

Table 1. *Results of Sympathetic Block in Poliomyelitis.*

Case No.	Age	Symptoms	Onset of Disease	Duration	No. of Blocks	Oscillometric Measurement		Result
						Before Block	After Block	
	yr.			mo.				
1	25	Marked spasm and tenderness of gastrocnemius muscle, with throbbing pain	December, 1945 (Philippine Islands)	4	4	2.5-3	6-8	Relief of spasm, tenderness and pain
2	19	Hyperhidrosis of hands; spasm and tenderness of right arm.	April, 1946 (Philippine Islands)	2	2	—	—	Relief of spasm and tenderness; hands dry.
3	32	Severe pain and tenderness	July, 1946 (Mississippi)	—	2	5-6	6-7	Relief of spasm, tenderness and pain; feet warm and dry.
4	39	Bilateral cyanosis, sweating and coldness; chilblains and edema.	September, 1945	3	6	2-3	7-7.5	Relief of paresthesias and improvement of edema; feet warm, pink and dry, with occasional cyanosis on dependency.
5	31	Marked coldness and bilateral hyperhidrosis	December, 1945 (India)	7	2	1-1.5	4-4.5	Feet warm and dry
6	24	Marked cyanosis, coldness and sweating, with paresthesias and some pain	March, 1945 (Tunis)	10	3	2	5.5-7	Relief of paresthesias; feet warm, dry and pink.
7	23	Marked cyanosis; coldness and sweating.	August, 1945	6	—	1-1.5	3-4	Feet warm and dry
8	26	Marked cyanosis; moderate coldness and sweating.	August, 1940 (New York)	60	3	4-3	6-7.5	Feet warm and pink
9	22	Marked coldness and sweating, with moderate cyanosis of both feet	August, 1945 (France)	6	3	3.5-4	6-7	Feet warm and dry
10	—	Marked coldness and cyanosis; moderate sweating; some paresthesias.	June, 1945 (Italy)	7	4	—	—	Relief of paresthesias; feet warm and dry.
11	39	Moderate coldness and sweating, with some cyanosis; mild paresthesias.	April, 1945 (Philippine Islands)	9	2	— —	— —	Relief of paresthesias; feet warm and dry.
12	21	Paresthesias of legs	August, 1945 (New Jersey)	7	3	—	—	Relief of paresthesias
13	24	Moderate edema, cyanosis and coldness	July, 1945 (Texas)	7	2	—	—	Progressively diminishing edema to normal in four weeks
14	27	Marked cyanosis and coldness; moderate sweating and edema.	September, 1945	6	3	1.5-2.5	4-5	Feet warm, dry and pink; progressively diminishing edema for three weeks.
15	27	Marked sweating and paresthesias; moderate cyanosis and coldness.	June, 1945	8	2	—	—	Relief of paresthesias after four months; feet warm and dry.
16	33	Hyperhidrosis, marked coldness and moderate cyanosis	June, 1945 (England)	8	2	1	3-4	Feet warm and dry
17	21	Marked edema, cyanosis, coldness and sweating of feet	April, 1945 (United States)	—	3	1-1.5	5-6	Improvement of edema; feet warm and dry.

one was rapid and intense. Diminution in sweating occurred slowly, but a dry extremity was usually found within twenty minutes.

Edema cleared up slowly in all cases. Three patients remarked that on the day following their first sympathetic block they could get into a slipper easily. Generally, however, swelling diminished after the second block and continued thereafter. In Case 4 circumferential measurements of the left ankle showed a change from 33.6 cm. before the first block to 28.5 cm. eighteen days later. The right ankle diminished in size from 31.7 cm. to 27.3 cm. over a period of thirty days.

Oscillometric recordings were made at the ankle of many patients. Readings made prior to injection gave an average excursion of 1.5, with a range from 0.5 to 2.5. Post-block recordings in all patients were increased. The excursions varied from 4.0 to 9.0 with an average reading of 5.0. Thus, there was an average increase of 3.5 over the preblock measurements.

Of unusual significance were the observations on 3 patients with spasm, tenderness and pain, and these cases are therefore presented in detail.

CASE 1. A 25-year-old Army nurse contracted poliomyelitis in the Philippine Islands in February, 1946, with paresis of the hamstring, gastrocnemius and soleus muscles bilaterally. She was transferred to the Army and Navy General Hospital in April, 1946. Her chief complaint on arrival was not the paresis but the severe pain, tenderness and muscle spasm involving the hamstring, gastrocnemius and soleus muscles. Because of the slight edema, dusky coloration and coldness of the feet paravertebral sympathetic lumbar blocks were performed. Following the first block on May 29 there was temporary relief of the vasospastic phenomena on the more affected side, but there was complete relief of the pain and muscle spasm lasting for 20 days, whereas on the unblocked side the symptoms were still marked. Subsequent blocks of both right and left sympathetic ganglions resulted in complete relief. This relief persisted, and the patient was sent home on convalescent leave on July 25.

CASE 2. A 20-year-old soldier contracted anterior poliomyelitis on April 16, 1946, while on shipboard returning to the United States from the Philippines. The chief manifestations were in the shoulder girdle, with particular involvement of the deltoid and triceps muscles. Later, weakness of the lower muscle groups, especially the quadriceps, developed. The patient was at first treated with hot packs and passive exercises. He was transferred to the Army and Navy General Hospital on May 30.

On June 4 tenderness and spasm were present in the biceps and triceps muscles of the right side. Stellate-ganglion block performed on the right resulted in an intense Horner's syndrome; the right arm and hand became dry and hot. Subsequent to the block the patient was amazed at the new and improved feeling in the right arm. He stated, "My right arm is now better than my left." Objectively, there was absence of tenderness and no detectable spasm. A second block was performed 2 days later, and the improved state had continued at this writing.

CASE 3. A 32-year-old staff sergeant contracted poliomyelitis on July 9, 1946, in Louisiana. He was transferred to the hospital on July 25. Physical examination revealed bilateral lower-extremity paresis, complete on the right and partial on the left. The chief complaint at that time was extreme pain, tenderness and muscle spasm that kept the patient awake at night. The right lumbar sympathetic ganglions were blocked on July 29, and there was subsequently little tenderness or pain. For the first time since the onset of the illness the patient had a good night's sleep and did not require analgesics. A second block 2 days later resulted in further improvement. Hot packs had been used initially, but only the expected mild comfort was obtained, whereas following the blocks improvement was sharp and definite.

DISCUSSION

The cause of vasomotor disturbances in poliomyelitis has not been completely explained. The intensity of such disturbances is variable, and although a patient may have extensive paralysis, the vasomotor changes do not necessarily parallel the paralysis. Neuropathologically, there is involvement of the intermediolateral cell columns whence the efferent preganglionic fibers arise to pass by way of white rami communicantes to the sympathetic trunk and ganglions. The postganglionic fibers passing via the gray rami are distributed to the vascular system. By alteration in the blood supply to a region the trophic state of the tissues and their metabolism can be influenced. In view of this, Harris[4] performed sympathectomy with the purpose of promoting the blood supply thereby accelerating bone growth. He noted that sympathectomy resulted in a warm, dry, pink extremity and also that bone growth was apparently enhanced.

In 1933 Ogilvie[5] reported on sympathectomy for the treatment of vasomotor and sudomotor disturbances in poliomyelitis. In 4 cases lumbar sympathectomy resulted in warm, dry and pink extremities, but this state was only temporary.

In 1934 Robertson[6] reported on the use of sympathectomy in 68 children with poliomyelitis in the chronic stage. The immediate results were good in the majority of cases, and although a long follow-up period was not possible in every case, several patients had warm, dry and pink extremities at the end of five years.

In the present series of cases with treatment by chemical sympathectomy the results were encouraging (Table 1). Several patients followed for six months after the course of blocks demonstrated continued relief. It is believed that if there is a severe recurrence of vasomotor disturbance, further blocks will be beneficial, and the patients have been so advised. Because of these encouraging results in adults, the question of sympathetic nerve block in children arises. From the standpoint of the anesthesiologist complete co-operation on the part of the patient is needed for successful regional block procedures. This is difficult to obtain in children, but the results in adults are considered to warrant a trial in children, and it is recommended that the cases be selected carefully and attention paid to good premedication.

The problem of treatment of muscle spasm also deserves further investigation. Most textbooks state that muscle spasm subsides in four to eight weeks, but experience with over 130 adult patients with poliomyelitis indicates that spasm and muscle tenderness may persist for several months, and these cases are not exceptional. Hansson and Straub[7] reported

that 21 of 158 cases in New York had varying degrees of muscle spasm eight months after the acute illness. These workers also stated that they had no specific remedy for muscle spasm. In view of the results in 3 of our cases it seems probable that impulses producing pain and spasm are mediated in part by the sympathetic system and that relief can be obtained by sympathetic nerve blocks. It is also suggested that sympathetic blocks may relieve the pain, spasm and muscle tenderness in the acute phase of poliomyelitis as dramatically as it did in our 2 cases in the convalescent stage and 1 case in the acute stage. Therefore, with this report as a background, it is hoped that further investigations will be carried out to determine the status of sympathetic blocks and their efficacy in poliomyelitis.

Summary

Vasomotor disturbances, such as edema, hyperhidrosis, coldness and chilblains, are frequently encountered in the convalescent period of poliomyelitis.

Sympathetic nerve blocks were employed to alleviate these distressing manifestations of disturbed vasomotor activity with partial to complete relief in 15 cases.

Pain, muscle spasm and muscle tenderness were completely relieved in 3 cases by sympathetic nerve blocks and without supplementary therapeutic measures, such as physiotherapy and hot packs.

It is suggested that the pain, tenderness and muscle spasm in the acute phase of poliomyelitis may also be alleviated by sympathetic blocks.

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AN ERUPTIVE FEVER INVOLVING THE SKIN AND MUCOUS MEMBRANES (STEVENS-JOHNSON DISEASE)*

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BALTIMORE

In 1866 von Hebra[1] first described erythema multiforme as a generalized skin eruption without marked systemic symptoms; a rare type with fever, malaise, prostration and an accompanying severe stomatitis and purulent conjunctivitis was mentioned. Kaposi,[2] in 1893, described an infrequent form with involvement of the mucous membranes. More recently, reports of erythema multiforme with occasional involvement of the mucous membranes of the eyes, mouth and genitalia have been presented.[3–8]

In 1922 Stevens and Johnson[9] reported 2 cases of "a new eruptive fever associated with stomatitis and ophthalmia." They believed that the features of their cases, although previously described as a rare form of erythema multiforme, justified consideration as a separate entity. Many strikingly similar cases have subsequently been reported. The almost identical clinical pictures certainly merit recognition as a distinct syndrome. The name "Stevens–Johnson disease" has been used by many writers for this clinical entity.

The disease is usually characterized at the onset by mild conjunctivitis and stomatitis, which are followed in one or two days by fever, prostration and a generalized erythematous skin rash that undergoes hemorrhagic or vesicular changes. By the end of the first week, the stomatitis becomes ulcerative or bullous, and the conjunctivitis severe, with a copious purulent discharge. Corneal ulceration with opacification or subsequent endophthalmitis is not infrequent. The usual period until resolution of the mucous-membrane lesions is two weeks. The skin lesions resolve in about three weeks. No known etiology of the disease has been established. Two fatal cases have been reported.

The following case is considered typical.

An 8-year-old boy of Italian descent was admitted to the hospital on May 15, 1945. Five days before admission, an upper respiratory infection with burning, watery eyes and a sore throat had developed. On the following day the mouth became exquisitely tender, and the upper lip swollen, with several small blisters; simultaneously, a discrete, purplish, macular, dime-sized lesion on the left forearm and an identical one on the abdomen were noted. Three days before admission the eyes became acutely inflamed and swollen. A physician found the temperature to be 102°F., and the patient was started on sulfadiazine. On the following day, burning on urination and soreness about the glans penis were noted. Sulfadiazine was continued during the 3 days prior to admission. The temperature remained elevated between 101 and 102°F. The stomatitis, conjunctivitis, and balanitis became more intense, and on admission, the violaceous rash had become generalized. There was no history of the administration of other medications, including the sulfonamides. The past history revealed the usual childhood diseases.

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There was no history of allergy. The family history was noncontributory.

Physical examination disclosed a patient who appeared acutely ill and shielded the eyes from the light. The skin of both the upper and lower extremities and the trunk was covered with a maculopapular violaceous rash; each lesion had a discrete, rounded border and measured 5 to 20 mm. in diameter. Many of the lesions were vesicular, whereas others had a heavy hemorrhagic crust. The intervening skin appeared normal. The palpebral and bulbar conjunctivas were swollen and acutely inflamed; there was a copious purulent conjunctival discharge. The corneas were clear. The anterior nares were reddened and crusted. The lips and the oral mucous membrane were swollen and injected with several denuded and hemorrhagic lesions. The tongue was not involved. The skin about the glans penis was reddened,

FIGURE 1. *Photograph on Admission, Showing the Swollen Lids, Encrusted Lips and Erythematous Eruption.*

and a thick, yellowish exudate was present about the corona and urethral opening. The cervical and axillary lymph nodes were enlarged. The spleen was not palpable.

The rectal temperature was 102.2°F., and the pulse 128.

Examination of the blood showed a hemoglobin of 66 per cent and a white-cell count of 4350, with 30 per cent adult neutrophils, 18 per cent young forms, 12 per cent eosinophils, 26 per cent lymphocytes, 8 per cent monocytes and 4 per cent myelocytes. The platelet count was 40,000 by the Rees and Ecker method (normal, over 200,000). Examination of the urine revealed occasional white cells in the sediment. The stools were normal. The blood sulfadiazine level was 2.1 mg. per 100 cc. The prothrombin time was normal, as were the coagulation and bleeding times. Clot retraction was complete in 12 hours, and the clot was of fair quality. A Rumpel-Leede test was strongly positive. Agglutination tests for typhoid, paratyphoid and typhus fevers, brucella, infectious mononucleosis and tularemia were negative, as were nasopharyngeal, throat, blood and conjunctival cultures.

During the first 3 days, the conjunctivas were irrigated with boric acid solution, and general supportive care was given, including intravenous fluids and blood transfusions. The conjunctivitis became severer, and pseudodiphtheritic membranes covered the corneas and scleras. These membranes were easily removed with forceps, and the underlying corneas were clear. Conjunctival culture on the 4th hospital day showed only colonies of hemolytic *Staphylococcus aureus* and 10,000 units of intramuscular penicillin every 3 hours was begun, penicillin ophthalmic ointment being applied locally. The protective membranes gradually sloughed away during the 2nd week, and both corneas revealed ulcerations that subsequently underwent opacification. By that time, the skin eruption had taken on a purpuric character that was believed to be associated with the thrombopenia (counts of 40,000 to 80,000 platelets). Most of the skin lesions became vesiculated and then ruptured, yielding a clear fluid, after which the layers of skin became adherent and hemorrhagic crusts covered the lesions. The oral mucosa underwent vesicle formation and sloughed, leaving raw areas that bled easily. Cultures of the skin vesicles were repeatedly negative. A light growth of hemolytic *Staph. aureus* was occasionally cultured from the oral lesions. On the 4th day, the spleen was felt to be enlarged. The white-cell count remained below 5000 during the first 2 weeks, and an eosinophil count of 6 to 12 per cent persisted during that time. Stool examinations for parasites were negative. The balanitis had subsided completely by the end of the 2nd week. The crust over the skin began desquamating during the 2nd week, and by the 3rd week, the skin revealed only dark brown patches of pigmentation at the site of the former lesions. The oral mucosa began re-epithelializing and was completely healed by the 3rd week. The platelet counts remained below 100,000 for the most part. Clot retraction and clot quality were impaired in proportion to the thrombocytopenia. An electrocardiogram showed prominent Q waves in the limb leads, with a PR interval of 0.18 second.

The patient was observed for 11 weeks. During that time the skin pigmentation slowly faded. The corneal opacities cleared slightly. The initial course of penicillin was continued through the 11th day and then stopped for 9 days. Penicillin was resumed intramuscularly on the 20th day because of corneal ulceration and continued for 5 weeks. The temperature gradually fell to normal on the 4th day and remained normal during the hospital course. Shortly before discharge the patient developed acute pharyngitis, which cleared rapidly. He was discharged without symptoms, except for slight photophobia and impaired vision, on the 75th hospital day.

On follow-up in the ensuing 11 months, the skin pigmentation had gradually faded. The corneal opacities that had encroached on the central vision had remained at about the same density and necessitated placing of the child in a sight-saving class. Visual acuity on July 10, 1946, showed 20/60 bilaterally. Several small adhesions of the palpebral and bulbar conjunctivas remained but did not restrict motility. The platelet counts were normal. The child was in perfect health except for the visual defect.

Although Stevens–Johnson disease has been considered primarily pediatric, approximately a third of the cases reported since 1922 have occurred in patients over fifteen years of age,[9–39] the case reported by Jones et al.[22] having occurred in a fifty-six-year-old woman. The sex incidence is five to one in favor of male patients.

No known etiology for the disease has been established. A virus has been suggested, but no virus has been isolated. Jones and his associates[22] examined conjunctival and vaginal scrapings and found no virus inclusion bodies. Their complement-fixation studies of patients' blood with psittacosis antigen showed positive values in dilutions only up to 1:64. Givner and Ageloff[19] found no inclusion bodies in vesicular fluid from skin lesions. Cultures on chick embryos were also negative. Edgar and Syverton[16] injected vesicular fluid intracerebrally and intraperitoneally in rabbits, guinea pigs and mice, with no effects. Chick and Witzberger[12] reported a case and referred to 2 others of Vincent's stomatitis accompanied by erythema multiforme;

these cases, however, lacked ocular involvement. The authors suggested that Vincent's infection, associated with altered tissue sensitivity, is an etiologic factor in Stevens–Johnson disease. Oral smears in typical cases, however, have not shown the organism of that infection.

The blood picture is not characteristic. The white-cell count is usually normal or slightly elevated. The case reported above is the first to show a persistent leukopenia. It is interesting to note that in over half the reported cases, the skin eruption is described as hemorrhagic or purpuric at some time during the illness. The purpuric character of the lesions, which was prominent in the case presented above, is believed to have been associated with the thrombocytopenia. The possibility that low platelet counts existed in similar cases with purpuric tendencies should be considered, although no previous platelet studies have been reported. The patient in the case reported above received sulfadiazine during the seventy-two hours prior to admission; thrombopenia and leukopenia resulting from this medication are a remote possibility. The eosinophil count of 6 to 12 per cent is unexplained. In 3 other cases a moderate eosinophilia was reported.[15, 18, 28]

Two fatal cases have been reported in which the syndrome was associated with severe respiratory infections.[34] Serious ocular sequelae have frequently been reported. Corneal ulceration with opacification may result, and perforation of the globe with enophthalmitis and panophthalmitis is not infrequent.[11] This has necessitated enucleation in several cases. The stomatitis is usually vesicular or ulcerative, and the membrane sloughs, leaving a raw buccal and palatal surface. The severity of the stomatitis may necessitate parenteral feedings for several days. Involvement of the mucous membrane of the genitalia has been reported in approximately a fourth of the cases. The electrocardiographic changes are probably nonspecific and due to the prolonged febrile illness. Edgar and Syverton[15] reported auriculoventricular block, with changes in the ST segments, in a twelve-year-old patient.

Recurrences of the disease are not rare. In 1 of Edgar's cases, complete relapses occurred six months and eleven months after discharge.

There is no specific therapy for the condition. Penicillin administration to combat secondary infection, together with general supportive care, has given the best therapeutic results.

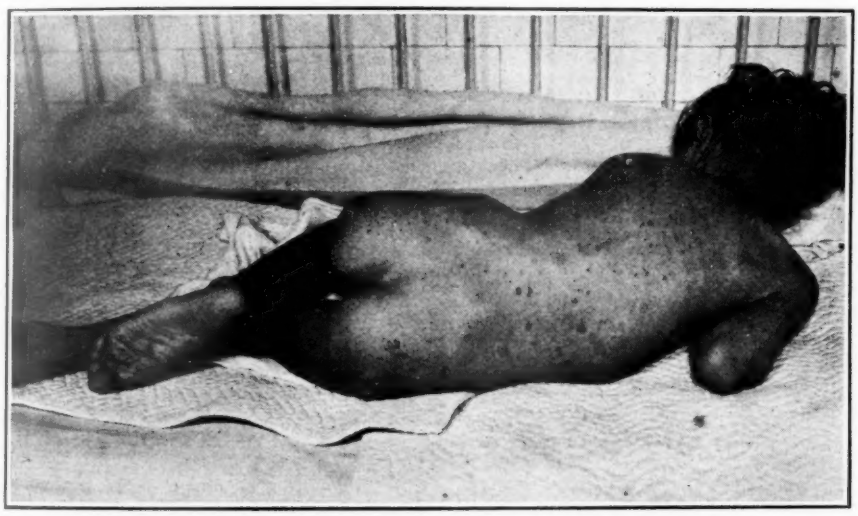

FIGURE 2. *Photograph Showing the Generalized Eruption.*

Several cumbersome names have been used to describe this entity, many cases being reported under the titles, "erythema multiforme bullosum with involvement of the mucous membranes," "mucosal respiratory syndrome" and "erythema multiforme pluriorificialis." Some observers maintain that the mucosal involvement is simply a symptom of erythema multiforme and that the syndrome should not be considered a distinct entity. Weisberg and Rosen[37] have championed this view. Since it is the enanthem rather than the exanthem that seems to be striking, regarding the disease simply as a symptom of erythema multiforme does not stress the more important features. Regardless of the name used, the recognition of the syndrome in its own right is essential.

SUMMARY

A review of the classic cases of erythema multiforme with mucous-membrane involvement (Stevens–Johnson disease) is presented.

A case with an erythematous skin eruption, associated with fever, a purulent conjunctivitis, severe stomatitis and balanitis is reported. Corneal ulceration with opacification was the only sequela. The course and clinical picture were almost identical with those in the cases described by Stevens and Johnson.

Persistent leukopenia and thrombocytopenia are reported for the first time in this syndrome.

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MEDICAL PROGRESS

STREPTOMYCIN*

I. Bacteriologic and Pharmacologic Aspects

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SEVERAL months have elapsed since streptomycin became available in this country for use in hospitals and then to physicians generally. Heralded at first as the final fruit of victory in the battle against bacterial infections, it seemed to be the obvious and natural supplement to penicillin and was to fill the few gaps among the infections that could not be disposed of by that potent agent. Experiences with penicillin, however, had conditioned the practitioner to expect from streptomycin brilliant, rapid and consistent results in susceptible infections and with essentially no untoward effects.

It soon became apparent, however, that none of these expectations would be entirely fulfilled and that considerable disappointment was inevitable. Streptomycin has, nevertheless, proved to be a useful agent, if properly employed, in certain types of infections. It seems desirable, therefore, to review the available information concerning this antibiotic and to define, so far as that information permits,¶ its field of usefulness and its limitations. The first part of this progress report deals with the properties of streptomycin, its pharmacology and its effect on bacteria in vitro and in experimental infections in animals. The results of its clinical uses in various infections will be considered in the second part.

DISCOVERY AND DEVELOPMENT

Streptomycin is the product of a search by Waksman and his associates[1, 2] for antagonistic organisms that are active against gram-negative bacteria. Certain actinomycetes, most of them isolated from soils or composts, were found to produce substances possessing marked antibacterial properties, but few of them offered chemotherapeutic potentialities. The first antibiotic that looked promising for the treatment of infections with gram-negative bacteria was streptothricin,[3, 4] which was active both in vitro and in vivo. Purified preparations of this substance, however, exerted a delayed toxic effect in animals and, in addition, certain important gram-negative bacilli were found to be naturally resistant to high concentrations.

At the same time, a search was also under way for antibiotics active against acid-fast bacilli. Certain fungi, notably *Aspergillus fumigatus*, were found capable of suppressing the growth of *Mycobacterium tuberculosis*.[5] Similar groups of organisms were therefore investigated. These combined studies resulted in the isolation of a strain of actinomyces from a heavily manured soil that was similar to one that Waksman had isolated in 1919 and had then classified under the name *Actinomyces griseus*.[1] The antibiotic, produced by the freshly isolated strain in a medium containing meat extract, resembled streptothricin in many respects but differed from the latter in that it had much greater activity against a number of pathogenic gram-negative bacteria and was free of many of its toxic effects in animals. The substance was called streptomycin, the name being derived from the generic designation given to the sporulating and aerial-mycelium producing group of actinomycetes — namely, the Streptomyces.[6]

Other antibiotics have been extracted from *Streptomyces griseus*.[7–10] One of them has antifungal activity,[7, 8] and another, called "grisein," has no antifungal properties and a narrower bacterial spectrum than streptomycin.[9]

Only certain strains of *Streptomyces griseus*, however, produce streptomycin.[9] The composition of the medium is also important.[2] Among other things, certain organic constituents supplied by the meat extract seem essential, but these can also be supplied by corn steep liquor and some other substances.[2, 10, 11] Aerated cultures produce maximum growth more rapidly than stationary ones. The medium becomes alkaline during the growth. Growth is terminated at the stage of maximum streptomycin production. The organisms are removed, and the antibiotic is extracted from the clear medium by adsorption on active charcoal. It is then eluted and extracted with suitable solvents and finally concentrated by desiccation in vacuo.[2] Further treatment is necessary to obtain the pure crystalline product, which is a white powder.[2, 12, 13]

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Aided by a grant from the United States Public Health Service.

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¶A number of contributions may have been overlooked or may not have been available at the time of this writing, and many more have appeared since this paper was completed and, therefore, could not be included.

Chemical Properties

Streptomycin was early recognized to be an organic base.[2] Crystalline reineckates were soon obtained, and tentative empirical formulas were derived from analyses of these salts.[14–16] Some studies of its structure have shown that it is composed of two main portions[17–21]: streptidine ($C_8H_{18}O_4N_6$), a basic substance, and streptobiosamine ($C_{12}H_{21-23}O_9N$), a nitrogen-containing disaccharide to which streptidine is joined through a glucoside linkage, which is readily split by methanolic hydrochloric acid.[17] Further information concerning the composition and structure of streptidine[18, 20–22] and the degradation products of streptobiosamine[22–25] has been revealed, but the final elucidation of the structure of streptomycin and its synthesis remains to be accomplished.

Streptomycin is a hygroscopic, optically active,[12] organic base, soluble in water but insoluble in the usual organic solvents. It forms salts with acids, and of these the soluble hydrochloride and sulfate are used clinically. The relatively insoluble helianthate is used in some methods of purification,[12] and the crystalline reineckate has been utilized for its characterization.[14] It is adsorbed on charcoal in alkali and may be eluted by acid.[2, 26, 27]

Streptomycin reacts with a number of carbonyl reagents.[17] It is readily oxidized to inactive streptomycinic acid by bromine.[22] Catalytic reduction by hydrogen results in dihydrostreptomycin,[28–30] which is a substance having antibiotic activity of the same order as streptomycin but which, in contrast to it, does not lose activity in the presence of cysteine or carbonyl reagents and is also stable at a higher hydrogen ion concentration.[29] Streptomycin reacts with alkaline copper solutions; urines containing 1000 units or more reduce Benedict's solution.[31]

Stability

Streptomycin is a relatively stable substance. Commercial samples containing less than 1 per cent of moisture show no loss of potency when stored at room temperature for a year.[32] It is also stable in solution at ordinary temperatures; there is no loss of activity in solutions at or below 28°C. at pH 3 to 7 over a period of sixty days, whereas it requires thirty-seven hours at 95°C. to reduce the activity of a solution at pH 5.5 to a half.[32] Buffered solutions containing 100 and 1000 units per cubic centimeter at pH 6.0, 7.0 and 8.0 are stable over a period of three months at 10°C.[33] Heating at 70°C. for thirty minutes produces no appreciable loss of activity.[34, 35] Less than 50 per cent loss occurs on heating at 100°C. for 10 minutes.[2] A marked increase in alkalinity causes rapid destruction, and boiling with normal sodium hydroxide for ten minutes results in complete inactivation.[23] No biologic agent or enzyme system has yet been found capable of destroying streptomycin.[36]

Assay

Units

Amounts of streptomycin are now expressed in terms of the weight of the pure base in grams, milligrams or micrograms.[37] Waksman[38] originally measured streptomycin in units, the unit being defined as the minimal amount of streptomycin activity that must be present in 1.0 cc. of nutrient medium to inhibit the growth of a given strain of *Escherichia coli*; this has also been called the "*Esch. coli* unit" or "S unit," which is approximately equivalent to 1.0 microgm.* He also proposed two other units: an "L unit," to indicate 1,000,000 S units, and a "G unit," to represent 1000 S units. These designations are no longer widely used. Commercial streptomycin is provided as the hydrochloride or sulfate, but the potency is expressed in terms of the weight of the pure base.[40]

Methods

Procedures that depend on the antibacterial properties of streptomycin have been widely used and form the basis of all the reported quantitative studies in patients. Most of them employ the same principles that are used in penicillin assay, with variations in the mediums and test organisms to suit the properties of streptomycin.

Streak-plate method.[41] This is a crude method that consists in the incorporation of graded dilutions of the material being tested in nutrient agar, followed by streaking of the surface with an array of organisms of known and graded sensitivity.

Agar-diffusion methods. These are modifications of the cylinder-plate technic[42] described for penicillin assay, and two main types are used. The first comprises the cup method, in which the material being assayed is placed in cups arranged on the surface of suitable agar plates seeded with a test organism. Stebbins and Robinson[43] used *Staphylococcus aureus* as the test organism. This procedure has been widely used and modified, and other test organisms — notably *Bacillus subtilis*[44, 45] — have been proposed. The second is the paper-disk method, which is a further modification of the first type, in which the assay cylinders are replaced by small paper disks moistened with the solutions being assayed.[46, 47]

Broth-dilution methods. Serial dilutions, usually twofold, are set up as in the penicillin assay method described by Rammelkamp.[48] The organisms generally used have been strains of *Klebsiella pneumoniae*,[49–51] *B. circulans*[52] and *Staph. aureus*,[53] and the inoculum is between 1000 and 100,000 organisms per cubic centimeter. End-points have been determined by turbidity or subculture, or both, on nutrient agar with or without inclusion of blood

*It is well to bear in mind that this unit has no relation to that of penicillin. The original Oxford unit of penicillin was defined as the amount required to inhibit 50 cc. of a staphylococcus culture. The international unit of penicillin is now defined as 0.6 microgm. of pure penicillin G.[39]

in the assay broth to act as an indicator of bacterial growth. Some authors have advocated the use of the least enriched medium that will give adequate growth.[51]

Slide-cell method.[35] The action of streptomycin is observed microscopically by its inhibition of growth of *B. megatherium* in defibrinated blood.

Turbidimetric method. Electrophotometric measurement of the turbidity of a staphylococcus culture containing streptomycin has also been used as a basis for assay.[54]

The results of these assays depend not only on variations in the methods used but also on such factors as the type and nutritive value of the medium,[51, 55–58] the salt concentration,[46, 58, 59] the hydrogen ion concentration,[34, 46, 60, 61] the test organism,[35, 43–45, 49–53] aerobic conditions,[36] the size of the inoculum,[57, 58, 60, 62] the time of incubation[57, 62] and factors that inhibit the test organism and are present in the medium[2, 34, 37, 49, 55, 56] or in the material being assayed.[49, 53, 58, 63, 64] This last factor may be quite important when *B. subtilis* is used, since it has been shown that a large proportion of human serums inhibit the growth of *B. subtilis* in varying degrees.[65] This effect may possibly be minimized by the use of citrated plasma instead of serum as in penicillin assay.[66] Uniform assay mediums have been proposed[45, 49] and are marketed, but their use is by no means universal.

Chemical methods of assay,[23, 67, 68] based on the properties of streptomycin or of its degradation products and not necessarily related to antibiotic activity, may have technical usefulness. For the present, however, biologic methods are the most satisfactory for clinical use.

Absorption, Excretion and Distribution

Absorption

Blood levels following intravenous and intramuscular administration of streptomycin have been extensively studied in man[44, 45, 69–75] and in animals.[47, 76–78] In general, maximum levels are attained a few minutes after intravenous injection, whereas after intramuscular injection of the same dose there is a gradual rise to a maximum in one or two hours.[69, 72, 78] At that time the levels are approximately the same for either method of administration, and there is a gradual falling off, with some evidence that the levels from the intramuscular injections are somewhat better sustained.[72, 73] The levels attained and the duration of detectable activity in the blood serum depend on the size of the dose, but are not directly proportional to it.[72] Table 1 shows serum levels attained at different times after various doses. These figures agree in the main with those reported by others, most of whom used similar assay methods — variations of the technic described by Stebbins and Robinson.[43]

Subcutaneous injections have not been widely used in human beings, but levels may be obtained that are only slightly lower than those following intramuscular administration.[69, 71, 73] Measurable levels of streptomycin may still be present in the blood twelve hours after a single injection of 200,000 units,[73] but therapeutic levels cannot be relied on after six hours in a normal subject.

Intermittent injections of suitable doses by any of these three parenteral routes every four to six hours will ensure the maintenance of desired levels. There may be some build up of levels after the first few successive injections.[69, 70, 72] An attempt to slow absorption from intramuscular injections by the use of streptomycin in beeswax and peanut oil or Solvecillin (a water-in-oil emulsion) gave inconclusive results.[79]

Table 1. *Serum Concentrations in Man after Various Doses of Streptomycin.**

Dose	Time after Intravenous or Intramuscular Dose		
units	*1 hr.*	*2 hr.*	*4 hr.*
25,000–50,000	1.5–2.5	1.0–2.5	0
200,000	10	6	3
400,000	10–15	8	6
500,000	15–20	15–20	10–15
1,000,000	25–50	25–45	15–25

*From Buggs et al.[72]

When streptomycin is given orally only small amounts appear in the blood and urine.[44, 45, 47, 69–71, 72, 78] The fecal concentration after oral administration is high,[44, 69] and almost all the administered streptomycin is recoverable in the feces, indicating that failure to enter the blood stream from the gastrointestinal tract is due to poor absorption rather than to destruction.[45] Artificial gastric or duodenal juice does not inactivate streptomycin.[70]

An appreciable concentration of streptomycin is still present in the cerebrospinal fluid twenty-four hours after an intrathecal injection of 20,000 units.[70] Similar results have been obtained by many workers.[71, 72, 80, 81]

Few reports are available on the absorption of streptomycin given as an aerosol. Detectable amounts are not present in venous blood, and only small amounts are found in the urine after inhalation of 200,000 units or less.[71, 73, 82] In a patient receiving 500,000 units daily, 6 per cent of the administered dose was found in the twenty-hour urine.[71]

Excretion

The bulk of the streptomycin excreted following parenteral administration is found in the urine, only a small fraction — 6 per cent or less — being found in the stools.[45, 69] Streptomycin has been recovered as an active colorless solid from the urine of dogs, according to Tennant, cited by Robinson.[83] Excretion in the urine is greatest during the two hours following a single intravenous or intramuscular

injection; up to 65 per cent is excreted in twelve hours, and 9 per cent more may appear during the following twelve hours.[73] The amount excreted in twenty-four hours is variously estimated as representing 17 to 90 per cent of the administered dose,[77] with averages of 57 to 66 per cent.[69] Only negligible amounts are recoverable from the urine after twenty-four hours.[44, 69, 71] Streptomycin is concentrated by the kidney, and high urine levels are easily attainable with therapeutic doses. The levels depend largely on the volume output of urine and have ranged from 120 to 2000 units per cubic centimeter,[50, 69, 71, 73, 84, 85] and even over 4000 units per cubic centimeter have been reported.[31, 85] The renal clearance of streptomycin has been studied, and the drug was found to be excreted by the glomeruli alone, 38 to 67 cc. of plasma being cleared per minute.[73] There may be diminished excretion and consequent concentration in the blood in patients with severe renal damage.[31, 72, 86]

Distribution

Following parenteral injection streptomycin is found in most of the body fluids and tissues. Concentrations are higher in the kidney than in the blood.[53, 73] The findings in other organs are irregular[47, 53, 73, 87] and probably unreliable. In mice, high concentrations are found in the liver and spleen if the streptomycin is given with trypan blue.[87] No demonstrable streptomycin was present in red cells hemolyzed by freezing, although the plasma removed from the same sample of blood showed a good level.[73] Streptomycin was not found in pus from soft-tissue abscesses in 4 cases.[53]

Spinal fluid. Most authors failed to demonstrate significant amounts of streptomycin in the cerebrospinal fluid even after large intravenous or intramuscular doses, when there was no meningeal inflammation,[69, 71–73] although 1 to 5 units per cubic centimeter may be found in the cerebrospinal fluid of patients with meningitis following similar injections.[69–73]

Pleural fluid. Levels found in the pleural fluid of patients with effusions, although somewhat lower,[53] may be better sustained than those attained in the blood.[69, 73] The appearance of streptomycin in pleural fluid is apparently slower if the fluid is thick.

Peritoneal fluid. The drug is found in the peritoneal fluid following parenteral administration, and the concentrations are usually less than those in the blood.[53, 69, 72, 73] Whereas most of the studies were made on patients with ascites, it has been shown that the agent readily enters the peritoneal fluid of normal dogs and of dogs with acute diffuse peritonitis.[88] Doses of 500,000 to 600,000 units intravenously or intramuscularly result in peak levels of 15 to 33 units per cubic centimeter.[83]

Bile. Numerous studies have been made on the presence of streptomycin in bile.[53, 69, 71, 73, 89, 90] The drug was found in the bile only when the cystic duct was patent. It does not seem to be concentrated by the liver, and levels in the bile are lower than those found in the blood. Impaired liver function results in lower levels or even absence of streptomycin in the bile. There is no evidence of absorption or concentration in the gall bladder.

Ocular fluids. In rabbits, good levels were readily achieved in the conjunctiva, sclera, extraocular muscles and aqueous humor following intravenous administration. Higher concentrations were attainable in secondary aqueous. Penetration to the aqueous was not accomplished by local instillations unless the cornea was damaged. High concentrations could be obtained by iontophoresis.[91] In a case of glaucoma[69] the secondary aqueous showed higher levels than the aqueous.

Fetal blood and amniotic fluid. Streptomycin readily passes through the placenta and is found in the fetal circulation.[71] Levels in umbilical-cord blood and amniotic fluid were approximately half those found in the maternal blood taken at the same time. Only negligible amounts were detected three hours after injection of the mother.[92]

Factors Influencing Action of Streptomycin in Vitro

Effect of reaction and number of organisms. The antibiotic effect of streptomycin is greater in an alkaline than in an acid medium.[34, 46, 60, 61] In addition, streptomycin activity is considerably decreased if the size of the inoculum is sufficiently increased.[57, 58, 60, 62] With an inoculum of 5000 or 10,000 organisms per cubic centimeter there may be a fourfold loss of activity with a change in reaction from pH 7.2 (at which activity is usually estimated) to pH 6.2 (a fairly usual reaction for pus). If, in addition, the inoculum is increased a thousandfold, the same change in reaction will decrease the activity sixteen to thirty-two times.[60] The effect of acidity is not due to destruction of streptomycin, since it can be restored by upward adjustment of the reaction.[61] These two factors may have contributed to some of the failures of streptomycin, as in cases of walled-off collections of pus.[74]

Effect of salts. The addition of many salts, such as sodium chloride, acetate and bicarbonate, potassium chloride and bicarbonate, lithium chloride and sulfate and some phosphates, has been found to increase the effect of streptomycin against *B. subtilis*.[46] Others,[58,59] however, noted a reduction in effect on certain organisms in the presence of increased salt concentrations, but their observations were made under different conditions. The salts in normal urine did not decrease streptomycin activity.[58]

Effect of glucose. Glucose reduces the activity of streptomycin.[2, 34, 58] The potency of streptomycin in agar is reduced to a half in the presence of 2 mg. in 10 cc. This effect is probably related to the pro-

duction of acid.[36] When a glycine buffer of pH 8 is present, no inactivation occurs. Glycine itself has no demonstrable effect on streptomycin.[36]

Effect of aerobic and anaerobic conditions. The action of streptomycin on facultative anaerobes is reduced if they are grown in an atmosphere of hydrogen or nitrogen instead of air and is almost completely abolished in carbon dioxide. These changes are related to the reaction and are prevented, in carbon dioxide, by the addition of potassium bicarbonate to the agar.[36]

Inactivation by chemical substances. The inhibitory and inactivating effect of a number of chemical substances has been studied.[17,36, 93–96] Cysteine inactivates streptomycin, and this effect is reversible by iodine.[93] Among other substances tested, 2-aminoethanediol caused inactivation.[93] Thioglycollic acid may also cause inactivation,[56, 96] but this may be due to the presence of glucose in the thioglycollate medium[36] or to an effect on the oxidation-reduction potential.[56] Among oxidizing and reducing agents that have been tested potassium permanganate and potassium periodate were the most effective in destroying the antibiotic activity of streptomycin.[95] Vitamin C[36] and carbonyl compounds,[17] such as hydroxylamine, semicarbazide, phenylhydrazine and methylphenylhydrazine, may reduce its activity. About 98 per cent inactivation is attainable at pH 5.3 with semicarbazide, and this substance has been proposed for use in the sterility testing of concentrated streptomycin solutions.[97]

Effect of body fluids. The action of streptomycin on staphylococci was not appreciably influenced by serous body fluids, pus or normal tissue juices.[61] Incubation of the drug with artificial gastric or duodenal juice had no appreciable effect on its activity.[70] Defibrinated blood and normal urine, likewise, did not decrease the activity.[58] Some reduction in activity was noted, however, in human serum.[58] The effect varies with the organism and with the concentration of the serum. Serum may enhance the activity of streptomycin against *Esch. coli*[63, 64] or *K. pneumoniae*,[49] whereas it inhibits this action against various organisms including *Staph. aureus* and *Streptococcus haemolyticus*,[63, 64] and it does not affect the sensitivity of Brucella.[62] Possibly, these conflicting results are due to differences in the methods used. Their clinical significance is not clear.

Table 2. *Sensitivity of Various Organisms to Streptomycin.*

Organism*	Reported Sensitivity† range	most frequent
Actinomyces bovis[2]	4	
Aerobacter aerogenes[1, 50, 52, 74, 85, 93, 98, 102, 110, 111]	0.5–128	6–25
Bacillus anthracis[2, 52]	0.5	
Bacillus cereus[1, 52]	0.8–2	
Bacillus megatherium[1, 2, 52]	0.25–8	
Bacillus subtilis[1, 52, 74, 82]	0.1–128	1–8
Brucella abortus[2, 62, 84, 113]	0.5–4	
Brucella melitensis[2, 52, 62, 84]	0.5–2	
Brucella suis[2, 62, 84]	0.5–3	
Clostridium perfringens (Welch bacillus)[102]	>104	
Clostridium septicum (*Vibrion septique*)[102]	>105	
Clostridium sordelli[102]	>105	
Clostridium tetani[102]	>104	
Coccidioides immitis[112]	>300	
Corynebacterium diphtheriae[2, 52]	0.4–4	
Diplococcus pneumoniae (pneumococcus)[50, 52, 53, 102]	4–50	
Diphtheroids[52, 110]	1–>128	
Eberthella typhosa[2, 52, 82, 84, 102]	1–120	1–16
Erysipelothrix muriseptica[114]	2.5	
Escherichia coli (various strains)[2, 10, 50, 52, 74, 85, 110, 111]	0.3–128	<8
Haemophilus ducreyi (chancroid)[115, 116]	1–5	
Haemophilus hemolyticus[117]	0.8–3	
Haemophilus influensae (Pfeiffer's bacillus)[2, 50, 52, 81, 82, 118–120]	1–50	1–5
Haemophilus parainfluenzae[115]	2.5	
Haemophilus pertussis[2, 121]	1–15	1–3
Histoplasma capsulatum[122]	>2500	
Klebsiella ozaenae[2, 52]	0.2–1.5	
Klebsiella pneumoniae (Friedländer's bacillus)[50, 52, 74, 82, 85, 111, 123]	0.2–128	0.6–8
Listerella monocytogenes[1, 2]	2.5	
Malleomyces mallei (glanders)[2]	10–>10	
Mycobacterium tuberculosis (avian)[124, 125]	10–50	
Mycobacterium tuberculosis (human and bovine)[107, 124, 126–128]	0.1–1	
Neisseria catarrhalis[129]	1–4	
Neisseria gonorrhoeae (gonococcus)[2, 115, 127]	5–40	10–15
Neisseria intracellularis (meningococcus)[2, 82, 127]	1–40	
Nocardia[124]	4–12.5	
Pasteurella pestis (plague)[2, 82, 130]	0.5–1.5	
Pasteurella tularensis[2, 130]	0.1–0.3	
Paracolon bacillus[50, 52]	2–128	2–16
Proteus morgani[52, 81, 84]	1–128	8–50
Proteus vulgaris[50, 52, 80, 85, 99, 110, 111]	0.4–128	4–25
Pseudomonas aeruginosa (*Bacillus pyocyaneus*)[1, 50, 52, 74, 82, 84, 110, 111, 116]	2–200	8–50
Salmonella (various species)[2, 52, 99, 102]	4–120	4–32
Sarcina lutea[1]	0.25	
Serratia marcesens (*Bacillus prodigiosus*)[2, 52]	1–64	
Shigella (various species)[2, 52, 59, 82, 102]	0.2–8	3–7
Staphylococcus albus[52, 74, 110]	1–256	1–4
Staphylococcus aureus[52, 74, 82, 92, 102, 110]	0.5–>128	1–8
Streptococcus faecalis[2, 52, 111]	12.5–60	
Streptococcus haemolyticus[52, 82, 102, 110]	1–>128	2–32
Streptococcus nonhemolytic[52]	1–>128	1–32
Streptococcus viridans[52, 92, 102, 110, 112]	0.1–>128	1–32
Streptomyces (various species)[124]	0.4–12.5	
Veillonella gazogenes[125]	10	
Vibrio comma (cholera)[124]	5–V500	

*A few additional organisms are listed by Waksman and Schatz[2] and by Pulaski and Sprinz.[52] Additional fungi are mentioned by Robinson[109] and Reilly.[109]

†Minimum inhibiting concentration of streptomycin in micrograms per cubic centimeter of culture.

Mechanism of Action

Streptomycin is generally bacteriostatic for susceptible organisms in low concentrations and bactericidal at higher levels.[2, 98–101] Microscopical examinations of organisms growing in subinhibitory levels of streptomycin have shown morphologic changes.[102] Large bizarre forms were noted in the study of *Eberthella typhosa*[104] and *Pasteurella tularensis*,[105] whereas marked elongation was noted with *Shigella sonnei* and to a lesser extent with *Salmonella typhimurium*, *Aerobacter aerogenes* and *Proteus ammoniae*.[101] Streptomycin has a bactericidal action both on growing cultures and on resting or nonmultiplying cells,[100, 101, 106] although this may not be true of its action on tubercle bacilli.[107] This bactericidal action is more marked against young cultures than against older ones.[36] Streptomycin has no effect on tetanus toxin.[108]

There is as yet no clear evidence to indicate just how streptomycin acts. Some antibiotics are adsorbed on the surface of bacterial cells, but this is apparently not true with streptomycin, at least so far as *B. subtilis* and *Staph. aureus* are concerned.[98] It has been suggested that streptomycin acts by the combination of its guanido groups with

nucleic acid.[109] Another possibility is that streptomycin acts by coupling with thiol groups that are biologically essential to the bacterial cells.[94]

Effect in Vitro and in Experimental Infections

In Vitro

Streptomycin has been shown to be bacteriostatic and bactericidal in vitro for a large number of gram-negative and gram-positive bacteria and for *Myco. tuberculosis*. The range of sensitivity of a variety of organisms is presented in Table 2. Streptomycin is ineffective or has a limited effect against some spores,[100, 135] and the gram-positive spore-forming pathogenic anaerobes are resistant,[102] as are most of the fungi,[7, 102, 103, 113, 122] viruses[136–138] and protozoa[139–142] that have been studied. Another antibiotic isolated from streptomycin-producing strains of *Streptomyces griseus* exerts an antifungal effect on *Cryptococcus neoformans* and on some nonpathogenic strains.[7, 8]

In a consideration of the probable effectiveness of a chemotherapeutic agent against a particular micro-organism, it is customary to include the sensitivity or susceptibility of the organism to the agent in vitro and the effect of the agent on the course of experimental infections in suitable animals.

Sensitivity in vitro is usually expressed as the minimum effective or inhibiting concentration (M. E. C. or M. I. C.), and this is determined by a suitably devised experiment in which large numbers of organisms are pitted against various concentrations of streptomycin in a medium suited to the growth requirements of the organism. Such factors as reaction, size of inoculum, time of incubation and use of solid or liquid mediums vary according to circumstances and from worker to worker. Thus, it is difficult to compare the reported sensitivities obtained from different laboratories. Furthermore, since it has been shown that different strains of the same bacterial species may vary greatly in their susceptibility to streptomycin and since sensitivities are usually determined on material obtained by a single colony selection,* the figures can be accepted as showing merely the range or order of sensitivity. Some organisms such as *Past. tularensis* and *Myco. tuberculosis* are extremely sensitive, whereas others, such as *Pseudomonas aeruginosa*, may be just within the limits of the streptomycin levels attainable in the body.

Therapeutic correlations. Some aspects of the correlation of in vitro sensitivity with the therapeutic value of streptomycin based on observations with *Haemophilus influenzae* are discussed by Alexander.[57] She suggests that sensitivity figures show the best agreement with therapeutic results if they are obtained by the use of large inoculums, mediums designed for optimal growth and an adequate growth period. An unpredictable factor involved in the lack of such a correlation is the emergence of resistant strains during treatment. There are others, as evidenced by the fact that treatment of infections in man due to various strains of Brucella and Salmonella and to *E. typhosa* have been disappointing despite apparently favorable in vitro sensitivity values, adequate blood levels and failure to demonstrate the development of resistance.[45, 62, 145]

Experimental Infections

Bacterial infections. The protective action of streptomycin, in adequate dosage, for experimentally infected animals has been demonstrated with staphylococci,[102] pneumococci,[102] species of Salmonella,[102, 146] *H. influenzae*[120] and meningococci.[127] The drug has been used for clearing mouse colonies of Salmonella infections.[147]

The results in certain experimental infections are of interest. In experimental typhoid infections in mice the mortality rate was higher among infected animals receiving small doses of streptomycin than in similarly infected controls. Larger doses, however, were protective.[104] Infections with *Brucella abortus* in chick embryos were controlled,[146] and those in most guinea pigs were eliminated if adequate streptomycin therapy was instituted within a week.[112] Infections with *S. schottmülleri* and *Ps. aeruginosa* in mice, with *S. gallinarum* in chick embryos and *Proteus vulgaris* in animals were also prevented.[146] Chick embryos were also protected against *Pr. vulgaris* infections.[148] The course of infection in mice with *Pasteurella pestis* was favorably influenced, and the streptomycin effect was similar to that produced by sulfadiazine.[128, 149] Streptomycin protected mice completely against fatal doses of *P. tularensis*.[129]† Some protective therapeutic effect was noted against *H. pertussis* in mice.[121, 150]

Streptomycin prolonged the life of mice experimentally infected with *Clostridium perfringens*.[151] Streptomycin resulted in the survival of 92 per cent of mice infected with anthrax as against 58 per cent with penicillin and 5 per cent with sulfadiazine.[152] There was only a slight effect on *Erysipelothrix rhusiopathiae* (erysipeloid) infections in mice—much less than that with penicillin.[153] Streptomycin seemed to be chemotherapeutically active against infections in rats with pleuropneumonia-like organisms and was more effective than gold compounds in the treatment of the associated arthritis.[154]

Extensive studies on experimental infections caused by *Myco. tuberculosis* have been carried out in guinea pigs,[126, 155–157] mice[158, 159] and chick embryos.[160] Streptomycin was shown to exert a marked suppressive effect on experimental tuberculosis in these animals. Combined therapy using streptomycin with Promin[161, 162] or with Diasone[163] gave better results than any of these agents used singly.

*Infected urines or exudates may be planted directly on suitable agar plates containing graded concentrations of streptomycin, and the sensitivity of the infecting bacteria can thus be determined more promptly.[143] An in vivo sensitivity test employing the chick embryo has also been devised.[144]

†The effect varies with the dose and time of institution of therapy; latent infection without development of resistance is demonstrable in some surviving mice.[130]

Spirochetal infections. A considerable therapeutic effect was noted against *Borrelia novyi* (one of the organisms of relapsing fever) in mice and *Leptospira icterohaemorrhagiae* (the etiologic agent in Weil's disease) in Syrian hamsters; the effect in these infections, however, was less than that produced by penicillin.[164] A suppression of the infection in rabbits was caused by the Nichols strain of *Treponema pallidum* after prolonged therapy with large doses (200,000 units a day),[165, 166] but lower doses failed to suppress the infection.[167, 168]

Fungous infections. Streptomycin was ineffective against *Blastomyces dermatitidis* infections of chick embryos.[169]

Virus and rickettsial infections. Streptomycin failed to affect the multiplication of a number of strains of influenza A and B viruses[136, 137] and the viruses of psittacosis[170] and meningopneumonitis[171] in chick embryos. It was ineffective in the prophylaxis and treatment of experimental vaccinia in rabbits.[138] It was more active than penicillin against *Donovania granulomatis* in embryonated eggs.[172] Feline pneumonitis was not suppressed by streptomycin in vitro or in vivo.[173] In doses of 2 mg. per egg it suppressed the growth of the rickettsias of epidemic (louse-borne) and endemic (murine) typhus fever in chick embryos but had no effect against that of scrub typhus fever in the same amounts.[174] It also suppressed the growth of the virus of lymphogranuloma venereum in eggs.[175]

Protozoal infections. No action was noted against *Plasmodium cathamerium* in canaries[139] or *P. lophurae* in ducks.[139, 140] A slight suppressive action was noted against *P. gallinacium* in chicks.[139]

Laboratory Uses

Streptomycin has been used either alone or in conjunction with penicillin or sulfonamides, or both, to prevent contaminations by susceptible organisms in the course of isolation of various infectious agents,[176, 177] including viruses[136, 137] and protozoa.[141, 142] It has no effect on the embryo of the developing hen's egg, at least in the concentrations that have been used.[136, 137, 148, 176, 177]

Toxicity in Animals

A great deal of work has been done concerning the toxicity of streptomycin for animals, most of it by Molitor and his co-workers.[37] Administration of the drug produces acute and chronic toxic reactions, some of which deserve special mention.

Acute Toxicity

The toxicity of purified specimens of streptomycin is extremely low.[2, 37, 102] Acute toxicity in mice was evidenced by increased activity, dyspnea and respiratory failure. The LD_{50}* for mice, determined on two hundred lots of streptomycin, ranged from 350 to 700 mg. per kilogram of body weight in most cases. Differences in toxicity could not be correlated with the potency of the preparations studied. The LD_{50} for eight samples of highly purified streptomycin ranged from 75 to 300 mg. per kilogram of body weight when given intravenously and from 300 to 1250 mg. when given subcutaneously — a ratio of about 4:1. The LD_{50} for guinea pigs was 400 mg. per kilogram of body weight for a batch whose LD_{50} for mice was 600 mg.[37] Similar values in guinea pigs have been obtained by others.[161] Subcutaneous injection of 30 to 70 mg. per kilogram of body weight produced acute respiratory distress in monkeys.[37] Mice survived oral administration of 5000 mg. of pure streptomycin per kilogram of body weight, whereas doses of 1000 to 3000 mg. of crude concentrates per kilogram of body weight proved fatal.[37]

*Smallest amount killing 50 per cent of the animals within the test period.

Chronic Toxicity

Mice receiving up to a total of 1000 mg. per kilogram of body weight subcutaneously in six days appeared normal, as did rats after seventy-two days on 100 mg. daily and guinea pigs on amounts up to 60 mg. per day. No pathologic changes were noted in these animals.[37, 154†]

Rats developed nutritional deficiencies when fed large doses of streptomycin and purified diets for prolonged periods[178] but not with smaller doses[178] or when the diet contained essential growth factors.[179] The picture presented, which was similar to that observed in experimental biotin deficiency, responded to biotin therapy.[178] The bacterial content of the feces of these animals was markedly reduced.

Monkeys given large doses parenterally — 50 to 100 mg. per kilogram of body weight — exhibited proteinuria, and some showed bromsulfalein retention. Autopsies revealed a peculiar type of fatty infiltration of the kidneys and less often of the liver. There was evidence that this process is reversible.[37] Dogs given 50 to 100 mg. showed protein, casts and cells in the urine after one and a half to two weeks. Three of the dogs developed changes in gait and posture suggestive of labyrinthine or cerebellar disturbance,[37] a phenomenon that has also been noted in human beings.[180, 181] No obvious pathological changes were found in the central nervous systems of these dogs.[182]

An investigation of the antidiuretic properties of streptomycin was carried out following a report of urinary retention in man occurring after administration of the drug.[183] It was shown that this effect was associated with impurities but that pure streptomycin had no such effect.[37]

Local Effects

Instillation of a solution of streptomycin caused reddening of a rabbit's eye,[37, 184] but this disappeared within twelve to twenty-four hours when the solu-

†Slanetz (*Proc. Soc. Exper. Biol. & Med.* 63:451-453, 1946) observed no toxic effects in mice fed up to 1000 mg. daily, but a greater increase in weight occurred in second litters at higher dosage levels as compared with controls.

tion contained 500 to 1000 units per cubic centimeter.[37] Intradermal injection caused slight local reddening, whereas subcutaneous injection of some lots resulted in edema, hemorrhage and necrosis.[37] No serious local effects were noted after intramuscular injection in rabbits.[37, 184] Thromboses did not result from intravenous injections.[37] Rabbits receiving 100 mg. per kilogram of body weight intrapleurally showed areas of hemorrhage and fibrous adhesions.[37]

The application of 1250 units of streptomycin to the cerebral cortex of cats and monkeys has caused convulsive manifestations in 30 per cent of the animals tested. These effects were less marked than those produced by comparable amounts of penicillin, as judged by clinical and electroencephalographic observations. The cisternal injection of 2500 units or more in monkeys produced signs of severe cerebellar dysfunction manifested by unsteadiness, ataxia and inability to stand up, accompanied by spontaneous nystagmus and tremor of the head.[185] Rabbits tolerated 10 mg. of streptomycin per kilogram of body weight intracisternally in 0.5 cc. of distilled water, but respiratory failure and death resulted from a similar injection of 20 mg.[186]

Special Effects

Streptomycin exhibited a low toxicity for rabbit spleen in tissue culture,[187] whereas concentrations of 200 units per cubic centimeter were mildly inhibitory for fibroblasts and epithelial cells.[184] Toxicity for developing chick embryos is likewise low, as noted above.

Some of the toxic effects encountered in the experimental use of streptomycin, such as lipoid infiltration of the kidneys and liver in monkeys and the vestibular difficulties in dogs and man, seem to be caused by streptomycin itself. At least two other toxic effects are due to impurities. One of these impurities is a histamine-like substance that produces a vasodepressor action and has probably been responsible for many of the undesirable immediate effects. This action may be removed by incubation with histaminase.[37, 188] The same substance may also be responsible for the antidiuretic action noted with some batches.[37] A separate impurity, not yet identified, gives rise to the increased intravenous toxicity of some batches.[37]

Resistance to Streptomycin

It was pointed out above that different strains of the same organism may vary considerably in their sensitivity to streptomycin. Strains of considerable resistance may occur among species of bacteria that are predominantly sensitive. Even within a given strain, there may be great differences in the sensitivity of individual cells.

Development of Resistance in Vitro

It was early shown that organisms could develop increased resistance to streptomycin. Waksman[99] was able to increase the resistance of a strain of *Pr. vulgaris* by growing it in sublethal concentrations of streptomycin. Resistance is usually increased in vitro by exposing bacteria to increasing amounts in fluid or solid mediums, the medium chosen being one that would normally support good growth of the particular organisms. Experiments have also been carried out with urine as a culture medium.[111] The resistance of a variety of bacteria has been increased in relatively short periods with the use of one or another of these methods. The development of resistance has not been found to be associated with the production by the organism of a streptomycin-inhibiting substance analogous to penicillinase.[36, 61, 62]

The following bacteria have been found to develop resistance in vitro: staphylococci,[61, 189, 190] *Str. faecalis*,[111] meningococci,[127] gonococci,[127] *Esch. coli*,[111, 191] *A. aerogenes*,[111, 191] *K. pneumoniae*,[100, 191] species of Shigella,[59] paracolon bacilli,[191] *Pr. vulgaris*,[111, 191] *Ps. aeruginosa*,[111, 191] *H. influenzae*[120] and *Myco. tuberculosis* (human[107, 192] and avian[107] forms and a nonpathogenic strain of Mycobacterium[107]). The rate of increase in resistance is generally expressed by the number of transfers needed to habituate the organism to growing uninhibited in some arbitrarily chosen concentration. Resistance may be acquired rapidly, particularly by *Ps. aeruginosa*, meningococci and gonococci. Other organisms require a greater number of transfers, but less than fifty usually suffice in the majority of those studied.[127, 191] The development of in vitro resistance of tubercle bacilli to both streptomycin and sulfonamides was retarded when the organisms were exposed to both agents simultaneously.[107]

Most workers have not studied increases in resistance to levels greater than 1000 units per cubic centimeter because of the amount of streptomycin required. When this has been done, however, resistance to over 50,000[191] and even over 75,000[127] units per cubic centimeter was readily obtained. These values represent essentially the limit of workable concentrations. The rate of increase in resistance seemed to be more rapid on surface than in liquid mediums.[191]

Effect of Streptomycin on Infections Produced by Resistant Strains

Mice infected with lethal doses of strains of *Staph. aureus*,[61] *Myco. tuberculosis*,[126, 193] *H. influenzae*[14] and meningococci[127] that had been made resistant were not protected by large doses of streptomycin. Mice infected with the parent streptomycin-sensitive strains of similar virulence were protected, usually by small doses. Infections produced by the streptomycin-resistant strains of *Staph. aureus* were favorably influenced by penicillin.[61]

Morphologic and Cultural Properties of Resistant Bacteria

No changes were noted in the morphology of cells or colonies of gonococci or meningococci that had become resistant in vitro.[127] Loss of pigmentation and a reduction in the rate of carbohydrate fermentation were noted in two resistant strains of *Staph. aureus*.[190] Changes in colony forms have been noted in strains cultivated from urinary-tract infections that had become resistant during treatment. Some species of Proteus lost their spreading property.[194] A number of strains of Shigella showed atypical reactions in Russell's double-sugar medium after becoming resistant, but this aberration disappeared during the course of five to seven transfers through streptomycin-free mediums.[59]

Two strains of *K. pneumoniae* that had become resistant on repeated passage through streptomycin-containing liquid mediums failed to ferment saccharose or to grow on citrate mediums. The ability to ferment saccharose returned in one of these strains after repeated transfer through streptomycin-free broth. Corresponding strains that had developed resistance during treatment and those in which resistance was rapidly enhanced by serial transfers on solid mediums containing streptomycin did not show these changes.[191] Resistant strains of *Esch. coli* do not synthesize biotin so well as sensitive strains.[178]

One strain of Brucella that had become resistant during treatment showed two distinct forms: one grew fairly rapidly as a large colony but lost its characteristic biochemical reactions; the other grew slowly, formed smaller colonies, was more highly resistant and largely retained its morphologic and biochemical reactions. The former also showed some changes in morphology and staining properties as compared with the original sensitive strain. Growth of the resistant strain but not the sensitive ones was stimulated by sublethal concentrations of streptomycin.[62]

All these changes were much less striking than those observed in organisms becoming resistant to penicillin.[42, 195–197]

Persistence of Acquired Resistance

Present evidence suggests that resistance, once acquired, is usually a fairly stable property. Gonococci and meningococci that had acquired resistance by exposure to streptomycin in vitro retained their resistance over a period of three and a half months.[127] Five strains of Shigella remained resistant to over 1000 units per cubic centimeter when stored for six months at 4°C.,[59] and the same strains retained appreciable resistance after fifty transfers, although there was a distinct falling off in the resistance of some. Similar results were obtained with a series of strains having somewhat lower levels of resistance.[59] Strains of staphylococci showed some decrease in resistance after transfer through broth,[190] whereas strains of *Staph. aureus* resistant to 2500 units per cubic centimeter retained their ability to grow well in 1000 units per cubic centimeter after four months in the refrigerator, after several mouse passages and after being adapted to penicillin.[61] Strains of *Myco. tuberculosis* made resistant in vitro retained that resistance after repeated subculture in streptomycin-free mediums for four months.[107] Those obtained from patients under treatment remained resistant after residence in guinea pigs for ten weeks or more.[198] The resistance of a strain of *H. influenzae* was reduced considerably on subculture in streptomycin-free Leventhal broth.[120] The strain of *Br. abortus* referred to above retained its resistance during transfer in streptomycin-free mediums for three months.[62] Strains from urinary infections that became resistant during treatment have retained the same degree of resistance after a hundred transfers in a streptomycin-free medium.[117]

Reciprocal Sensitivity (Cross Resistance)

Organisms becoming resistant to one antibiotic may remain sensitive to another.[99] When *Staph. aureus* was made resistant to penicillin, streptomycin or streptothricin, a slight increase in resistance to streptomycin was noted in the organisms becoming resistant to streptothricin,[189] but no other reciprocal or cross resistance has usually been noted.[61, 189] In one study, however, it was noted that two of five strains of staphylococci developing resistance to penicillin increased in resistance to streptomycin, whereas five strains becoming fast to streptomycin remained sensitive to penicillin.[190] Streptomycin-resistant meningococci are susceptible to penicillin in vivo and in vitro, and meningococci made resistant to penicillin remain susceptible to streptomycin.[127] Gonococci that acquired resistance to either agent remained susceptible to the other in vitro, although one strain of gonococcus became more susceptible to streptomycin after it had acquired resistance to penicillin.[127] Organisms acquiring streptomycin resistance remain sensitive to sulfonamides.[107, 189]

Resistance and Virulence

There was no loss of virulence with increase of resistance in vitro of meningococci.[127] Strains of tubercle bacilli becoming resistant in vitro and in vivo remained virulent for mice[193] and guinea pigs.[107, 198]

Mechanism of Development of Resistance

The mechanism by which resistance to an antibacterial agent develops in a culture is still a matter for speculation. The possibilities that have been mentioned include: natural selection from a heterogeneous population; modification of the individual cell by establishment of alternative internal mechanisms within the cell or by qualitative or quantitative modifications of existing mechanisms, particularly enzyme systems; and changes in some center

of organization of the cell.[199] Demerec[200] has visualized two possible methods by which organisms may develop resistance to penicillin: by the acquisition of this characteristic through contact with the agent and as an inherited character originating through mutation. His experiments and those of Luria[201] suggest that the latter is the more probable method.

Highly resistant variants have been found in each of six strains of Shigella not previously exposed to streptomycin by subjecting large numbers of bacteria (up to eight billion) to the action of various concentrations of the antibiotic.[59] The ratio of resistant variants to total organisms was estimated at from 1:500,000,000 to 1:16,000,000,000, depending on the strain. Furthermore, susceptible organisms produced resistant variants in the same proportion, even after a series of six consecutive single-colony selections of presumably susceptible cells. A few variants of *A. aerogenes* and *K. pneumoniae* that were resistant to over 50,000 units per cubic centimeter were found to develop from inoculums of several billion relatively sensitive organisms on agar plates containing streptomycin.[191] The development of resistance to streptomycin, therefore, seems to be the result of the occurrence of resistant variants and subsequent selection by a high streptomycin concentration.

Washed cells of two strains of Shigella suspended in physiologic saline solution and exposed to streptomycin for seven days under varying conditions failed to show any increase in resistance to streptomycin.[59] The failure of *Esch. coli* in the resting state to develop resistance on exposure to streptomycin has also been demonstrated.[101]

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33191

PRESENTATION OF CASE

A seventy-eight-year-old widowed contractor was admitted to the hospital because of urinary frequency.

The patient had noted frequency, especially during cold weather, for over eight years. This had increased, until lately he had been voiding about every two hours during the day and once at night. He had had no dysuria, pyuria or hematuria. Following a recent cystoscopy the symptoms had become severer. On the morning of admission he was in a state of acute retention.

Physical examination showed slight enlargement of the heart. There was a soft, short systolic murmur at the apex and a loud rushing diastolic murmur that almost obscured the second sound. At the base there was a blowing systolic murmur, and the aortic second sound was not heard. The prostate was enlarged to twice the normal size. There was a moderate pitting edema of the ankles.

The blood pressure was 160 systolic, 85 diastolic.

Examination of the blood disclosed a hemoglobin of 14.8 gm. The urine was red and gave a +++ test for albumin, and the sediment contained innumerable red cells. The nonprotein nitrogen was 30 mg. per 100 cc. An x-ray film of the chest revealed a markedly enlarged heart, particularly in the region of the left ventricle. The aorta was tortuous and slightly dilated. An electrocardiogram revealed normal rhythm at a rate of 76 with considerable left-axis deviation, a low, diphasic T wave in Lead 1 and inverted T waves in Leads CF_4 and CF_5. A blood Hinton test was negative.

On the fourth hospital day a transurethral resection was performed. A moderate amount of bleeding was encountered. Near the end of the operation, the surgeon noticed a lack of return of irrigating fluid, and at the end of the operation it was noted that the abdomen was markedly distended. A suprapubic incision was made, and drainage of the peritoneal cavity and perivesical space was accomplished. Most of the fluid was anterior to the parietal peritoneum. At the end of the operation, the patient was in poor condition. Five per cent dextrose and water was given during the operation, and immediately postoperatively two transfusions were administered. For the following week there was almost no urinary output. The nonprotein nitrogen by the third postoperative day had risen to 128 mg. per 100 cc.; the serum protein was 5 gm. per 100 cc., and the chloride was 87 milliequiv. and the carbon dioxide 20.3 milliequiv. per liter. The suprapubic peritoneal drain was removed on the fifth postoperative day. The wound was in good condition, and peristalsis was noted. The nonprotein nitrogen, however, had risen to 185 mg. per 100 cc., the chloride had fallen to 77 milliequiv. and the carbon dioxide to 18.8 milliequiv. per liter. On the following day the nonprotein nitrogen was 195 mg. per 100 cc.; the chloride was 79 milliequiv. and the carbon dioxide 17.7 milliequiv. per liter. On the sixth postoperative day a right nephrostomy and renal decapsulation were performed, and cloudy fluid was drained from the retroperitoneal region. Culture of this fluid revealed abundant colon bacilli and a few nonhemolytic streptococci. Twenty-four hours after decapsulation the nephrostomy tube began draining water-clear urine in increasing but small amounts, and almost no urine was passed by way of the indwelling catheter in the bladder.

On the following day the patient suddenly became extremely short of breath and cyanotic. The neck veins were distended, the pulse was rapid, and rhonchi were heard in the chest. He was given aminophyllin, with dramatic improvement in breathing and color and some clearing of the chest signs. There were slight dullness and markedly diminished breath sounds at the right base, with some rales at both bases. On the next day the nonprotein nitrogen had reached 210 mg. per 100 cc., and the chloride 64 milliequiv. and the carbon dioxide 22.2 milliequiv. per liter. Two days later, the hemoglobin was 10 gm.; the blood calcium was 7.2 mg., the phosphorus 14.7 mg., the nonprotein nitrogen 240 mg. and the protein 6.2 gm. per 100 cc., and the chloride was 85 milliequiv., the carbon dioxide 19.4 milliequiv. and the sodium 13.3 milliequiv. per liter. On the next day a transfusion was administered. Twelve days after prostatectomy 450 cc. of light, clear urine was collected from the nephrostomy tube, and the dressing was wet, but the nonprotein nitrogen had risen to 260 mg. per 100 cc. On the following day the patient became extremely restless and expired.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES BURNETT: The primary problem is to explain the renal failure in this patient, who, following transurethral resection, became anuric, developed uremia and died thirteen days after operation. I think that it is clear that he had prostatic obstruction of long standing, with urinary retention, and that he had benign hypertension and heart disease.

May we see the x-ray films? Is there any evidence of left auricular enlargement?

DR. STANLEY M. WYMAN: In the lateral view the retrocardiac space is not obliterated, and there is prominence in the region of the left ventricle. The concavity of the auricle is maintained at this point.

DR. BURNETT: How about the aorta?

DR. WYMAN: It is tortuous, but I do not believe that it is dilated. The transverse diameter seems to be within normal limits for a person of this age.

DR. BURNETT: Is there any evidence of congestive failure?

DR. WYMAN: I do not believe so.

DR. BURNETT: I believe that the cardiac lesion was caused by hypertensive heart disease and calcareous aortic stenosis and that the mitral murmur heard at the apex was due to hypertrophy and dilatation of the left ventricle. The electrocardiogram is also consistent with this diagnosis. There was some evidence of congestive failure in that pitting edema of the legs was observed. The laboratory data on admission showed proteinuria and hematuria and a compensated renal function, at least so far as the nonprotein nitrogen was concerned. Beyond that we are not given any data that tell what the renal reserve was.

I should like to ask a few questions. What was the nature of the fluid used in the irrigating solution? Was any evidence of hemoglobinuria, hemoglobinemia or icterus noted at any time postoperatively? Were sulfonamides administered at any time?

DR. GEORGE G. SMITH: The fluid used was sterile tap water. The patient had not been given any sulfonamides except 1 gm. of sulfadiazine after I cystoscoped him in my office. He had no icterus. It is unfortunate that we do not know about hemoglobinemia because Dr. Woodruff has been checking that carefully on all transurethral prostatectomies, with interesting results. In this particular case he had the syringe ready, but in our haste to start the operation, he did not take the blood. Thus, in the one case in which we should particularly have liked to have a reading, no observation was made.

DR. BURNETT: From the description of the operation we may assume that a perforation of the bladder or the bladder neck had occurred. We are told that a considerable amount of bleeding was encountered and that the patient was in poor condition at the end of operation. Hence, he must have had at least some degree of shock, which I believe is the first factor that contributed to the fatal outcome.

Sterile tap water was used in the transurethral resection. It has recently been demonstrated by a number of workers that in this procedure a large number of veins are exposed in the prostatic bed, allowing ready access of the water to the veins and amounting to intravenous infusion of water, with the production of hemoglobinemia and renal failure. Dr. Joseph Ross[1] studied 23 cases recently, 15 of which developed hemoglobinemia, and in 6 the hemoglobinemia was of sufficient degree to produce hemoglobinuria. Two patients died, one of shock and the other of renal failure with a characteristic renal lesion. In this study the pressure of water used for irrigation was 100 mm. It is known that the pressure in the pelvic veins is 0–5 mm., and, indeed, in some cases it may be negative, so that it is not too surprising that intravascular hemolysis and hemoglobinemia result. This is a second factor that I believe to have contributed to the fatal outcome in the case under discussion.

The third factor is that two transfusions were given at the end of operation. We are not told whether a subsequent attempt was made to check the donors for the presence of incompatibility, but intravascular hemolysis of donor cells is always a possibility when a transfusion is given. Sulfonamides seem rather well excluded.

Hence, there were three factors capable of producing the hemoglobinuric or lower-nephron nephrosis that I believe was present in this case, and any one of these alone may produce it. Wounded battle casualties in severe shock and without any marked degree of pigment destruction have been shown to develop the lesion. The cause is thought to be partly renal ischemia, which is known to occur during shock and to persist for some time after recovery from shock. Hemolysis of one's own hemoglobin is known to produce the lesion if the hemolysis is of sufficient degree. Hemolysis of donor cells following transfusion of incompatible blood is too well known to require discussion.

The course in the case under discussion is compatible with such a diagnosis, as it is with any case of acute renal insufficiency. The progressive, severe azotemia, hypochloremia, acidosis, hypocalcemia, hyperphosphatemia and hyponatremia have all been seen and described in this syndrome. The episode on the eighth day may have represented pulmonary edema. In this particular type of acute renal insufficiency it has been demonstrated that the plasma volume is increased, — that is, that there is a true hydremia, — and I suspect that such an increase was present. The hypochloremia, as well as the fact that this man had a reduced cardiac reserve, readily explains the occurrence of acute pulmonary edema. Other possibilities are pulmonary infarction and atelectasis in the right lower lobe, as the signs suggested. The hemoglobin of 10 gm. on the tenth day as compared to 15 gm. on admission is confirmatory evidence of blood loss and possibly of a previous hemolysis.

The effect of decapsulation of the kidney is interesting. It appeared to increase the output of urine, especially on the side where it was done, and suggests that this procedure should be put to a fresh test in such cases.

I suppose that one must also consider a benign nephrosclerosis, which was probably present to some extent, and it seems conceivable that acute renal insufficiency developed following the insult of operation, with nothing more demonstrable at autopsy. The patient may have had pyelonephritis and old hydronephrosis secondary to long-standing prostatic obstruction. The third possibility is the condition of so-called "reflex anuria," which occurs following urologic procedures. The anuria is presumably neurogenic in origin, and at autopsy no lesion can be demonstrated. I had not considered either bilateral cortical necrosis or periarteritis nodosa in this case, but they are, I suppose, possibilities.

I believe that the patient had hemoglobinuric nephrosis, in addition to uremia, hypertensive heart disease, calcareous aortic stenosis, some congestive heart failure, possibly some peritonitis and probably retroperitoneal infection.

Dr. Tracy B. Mallory: Dr. Smith, will you tell us your impression of the case?

Dr. Smith: The over-all impression is a sad one. This case began to go wrong when the spinal anesthetic did not work. After resection was started, the patient had pain, which I did not think at that time was due to extravasation of the urine, since I had hardly begun to resect. He was given inhalation anesthesia, and I went ahead with the resection. If he had not been under general anesthesia we would undoubtedly have noticed the leakage of fluid sooner, because these patients under spinal anesthesia are aware of pain when the fluid extravasates around the bladder. I thought that the point of leakage of the fluid was from the roof of the urethra, and when the operation was concluded and the patient lay flat on the table, it was seen that he had a marked swelling of the suprapubic region, so that we prepared for an abdominal operation as soon as possible.

As soon as the perivesical space was entered there was the escape of much slightly blood-stained fluid, which seemed to come largely from the perivesical space and more from the right side than the left. The peritoneum was opened purposely because the symptoms at the conclusion of the resection, when the patient quickly came out of general anesthesia, suggested that he had some intraperitoneal fluid. A small amount of clear fluid was obtained from the peritoneum, whereas the fluid from the perivesical space was bloody. Therefore, it did not seem likely that the rupture had extended into or involved the peritoneal portion of the bladder. A small drain was placed in the peritoneum, however. The bladder was opened, and a hasty exploration of the dome of the bladder revealed no rupture. The bladder was drained by a suprapubic tube.

It is surprising that although the heart seems to have been seriously damaged it took a terrific beating and got him through twelve days of the hardest kind of going without failure. The case was handled carefully from the chemical point of view; Dr. Woodruff, the resident, followed the general rules of treatment in these cases that were laid down by Dr. George W. Thorn[2] in an admirable lecture that he gave before the Clinical Association of Genitourinary Surgeons. But it had become evident that the nonprotein nitrogen was going up steadily and rapidly, and the patient was still not excreting fluid. The experience that I had had with a few cases of anuria in the past indicated that decapsulation was certainly worth doing. The decapsulation and nephrostomy took about twenty minutes. The patient was much better the next morning, although he did not excrete fluid. He began to drain fluid two days after operation, but although 450 cc. of urine is a large enough output to enable a patient to get along without uremia if the urine is the product of a sufficient kidney, this was the product of an insufficient kidney with nephrosis of the lower nephrons. Nothing but water was being passed through the kidney. I suppose that if we could have kept him alive for another week or ten days the kidney tubular epithelium might have recovered enough so that he could have lived.

Clinical Diagnoses

Obstructing prostate.
Hemoglobinuric nephrosis.
Uremia.

Dr. Burnett's Diagnoses

Hemoglobinuric nephrosis.
Uremia.
Hypertensive heart disease.
Calcareous aortic stenosis.

Anatomical Diagnoses

Hemoglobinuric nephrosis.
Operative wounds: transurethral prostatectomy; drainage of perivesical space; and decapsulation of kidney.
Prostatic hyperplasia.
Endocarditis, chronic rheumatic, of aortic valve, with stenosis.
Hypertrophy of heart.
Arteriosclerosis, generalized, moderate.

Pathological Discussion

Dr. Mallory: As Dr. Smith has said, a biopsy of one kidney was done at the time of decapsulation. Characteristic precipitated-hemoglobin casts were observed in the distal convoluted tubules. The biopsy, of course, had to be limited to the surface of the kidney and showed only the cortex. The major lesion in these cases is seen in the pyramids.

At autopsy we found evidence of a full-blown lesion — a great many pigment casts throughout the lower segments of the nephron, degeneration of the epithelium of Henle's loops and interstitial in-

flammation. I could distinguish no difference between the kidney that had been decapsulated and its mate. The proximal convoluted tubules and glomeruli, as usual, were normal except for a mild degree of dilatation. The lesion was, of course, indistinguishable from that which follows a transfusion reaction.

Checking back over cases of transurethral resection done in this hospital during the last seven or eight years, Dr. Firminger has found 5 similar cases. There have been none in patients on whom suprapubic or perineal prostatectomy has been performed.

The heart was moderately hypertrophied, weighing 490 gm., and the aortic valve had enough interadherence of the commissures to have produced slight stenosis. The coronary arteries showed only slight atheroma. The lungs were moderately edematous, as had been expected.

References

1. Ross, J. Personal communication.
2. Thorn, G. W. Unpublished data.

CASE 33192

Presentation of Case

A sixty-four-year-old postmaster entered the hospital because of postprandial distress and regurgitation.

Two months before admission, following a drink of whisky, the patient had experienced the first episode of distress in the lower middle portion of the chest anteriorly, followed by regurgitation of some mucus. A short time later, the same thing happened after a swallow of ginger ale. During the next two weeks several similar episodes occurred; in the intervening periods he could swallow food and fluids without trouble. Six weeks before admission substernal distress and regurgitation of clear mucus began to follow swallowing of solids as well as fluids. On one occasion, while eating a tough piece of steak, he felt a sensation "as though a pineapple were being forced through an ulcer." He had reduced his diet, and in the two months he had lost 15 pounds.

Physical examination was essentially negative except for bilateral saphenous varicosities.

The temperature, pulse and respirations were normal, as was the blood pressure.

Routine examinations of the blood and urine were negative, and the total protein, nonprotein nitrogen, sugar and prothrombin time were normal, as was an electrocardiogram. A gastrointestinal series demonstrated a lobulated ulcerated tumor mass, measuring approximately 11 cm. in length, that involved the lower end of the esophagus and arose from its right posterior wall. It produced only slight obstruction to the flow of barium. The esophagus immediately above the diaphragm appeared free of tumor. The stomach showed no evidence of pathologic change.

On the fourth and eleventh hospital days blood Hinton tests were reported positive.

An operation was performed on the twelfth hospital day.

Differential Diagnosis

Dr. John B. McKittrick: In this patient with symptoms of two months' duration there had apparently been no history of previous trouble. The symptoms were characteristic of esophageal disease. I have the impression from the record that the symptoms were intermittent and that the inability to pass food down the esophagus was not steadily progressive. One fleetingly thinks of esophageal spasm or cardiospasm with such a history, but as a rule, cardiospasm is of longer duration, rarely appearing primarily in a sixty-four-year-old man.

The physical examination does not help a great deal, nor do the other studies that were done in the hospital prior to operation. The patient had lost considerable weight — 15 pounds — in two months on a starvation diet. The record does not specify what the diet was, but I assume that he had confined himself to food that he could swallow easily and that this was quite limited. Apparently, at that point, he had been eating solid food rather than liquid. In contradistinction to carcinoma, it might be mentioned that patients with esophageal spasm often swallow solid food better than liquid. Is that correct, Dr. Sweet?

Dr. Richard H. Sweet: I believe so; the symptoms are intermittent, at any rate.

Dr. McKittrick: As I read the record I was puzzled by the description of the x-ray examination and was not able to make a diagnosis. "A lobulated ulcerated tumor mass" — an unusual description — is mentioned. I suppose that a malignant tumor of the esophagus could be so described. I am interested to know whether this tumor showed evidence of infiltration in the wall of the esophagus or of peduncu-lation. Can infiltration of the wall of the esophagus be ruled out?

Dr. Stanley M. Wyman: Not without fluoroscopy. On the film, this must be what is described as the lobulated mass — large confluent masses of tissue obliterating the normal mucosal pattern. The ulcer that is spoken of is probably this shadow.

Dr. McKittrick: It is a sessile, ulcerated, lobulated tumor. I think that the only diagnosis that I can make is a malignant tumor of the esophagus. Tumors of this size can develop in the course of the short history that this patient gave. Carcinoma of the esophagus with few symptoms referable to the esophagus does occur. It is conceivable that tumors more obvious than this are less symptomatic. The two positive blood Hinton tests are interesting, but I do not believe that the x-ray picture is characteristic of syphilis of the esophagus. My diagnosis is

malignant tumor of the esophagus, probably an epidermoid carcinoma.

DR. CHESTER M. JONES: Is the cardia of the stomach perfectly intact?

DR. WYMAN: I believe that the extreme distal esophagus and the cardia are normal.

DR. JONES: In other words, it appears that the tumor did not originate in the stomach, progressing up the esophagus. If it was carcinoma, I should be more inclined to call it an adenocarcinoma.

DR. TRACY B. MALLORY: On what basis? Because of its polypoid rather than constrictive growth?

DR. JONES: Yes.

DR. MCKITTRICK: That is a pertinent suggestion and should have been considered in the diagnosis.

CLINICAL DIAGNOSIS

Carcinoma of esophagus.

DR. MCKITTRICK'S DIAGNOSIS

Malignant tumor of esophagus, probably epidermoid carcinoma.

ANATOMICAL DIAGNOSIS

Adenoacanthoma of cardia of stomach.

PATHOLOGICAL DISCUSSION

DR. SWEET: This was a polypoid type of tumor, which is associated with the adenocarcinoma group, and it was one of the group of cases in which the cardia was actually 4 or 5 cm. above the diaphragm. What looks like esophagus below the lesion was really stomach, so that this was a carcinoma of the cardia entirely above the diaphragm.

DR. MALLORY: The specimen that Dr. Sweet resected consisted of the lower part of the esophagus and the upper 7 cm. of the stomach. A cancer was found centered at the cardiac orifice and extending in both directions, up into the esophagus and down into the cardia of the stomach. It was an adenocarcinoma, which in a few areas showed foci of squamous-cell formation and therefore falls in the group of tumors with both adenocarcinoma and squamous-cell carcinoma that are called adenoacanthomas. I do not believe that it is possible to be dogmatic about whether the origin was on the esophageal or the gastric side of the cardia, although adenoacanthomas are rare in the stomach and occasionally seen in the esophagus.

The New England
Journal of Medicine
Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.00 per year (Boston funds); $8.50 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, three weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

COMING ANNUAL MEETING

The one hundred and sixty-sixth anniversary of the Massachusetts Medical Society will be held at the Hotel Statler, Boston, on May 20, 21 and 22, and the program of the meeting appears elsewhere in this issue of the *Journal*.

Owing to the fact that the program covers three full days, the meeting of the supervising censors and the annual meeting of the Council will be held in the late afternoon and early evening, respectively, on May 19.

The first general session will begin at 9:05 a.m. on May 20, and four papers will comprise a symposium on industrial medicine. The annual meeting of the Society will be called to order at 11:00 a.m. and will be followed by the annual oration, "Medical Care in Our Free Society," by Dr. Leland S. McKittrick, and by the annual luncheon. The second genera session will begin at 2:00 p.m. and will be devote to a symposium on the distribution of medical ca for the people of Massachusetts. The speakers a Drs. Elmer S. Bagnall, Charles F. Hayden an Winthrop Adams and Messrs. Reginald F. Cahalan and Jarvis Hunt. The topics to be discussed includ the attitude of the Massachusetts Medical Society Blue Cross and Blue Shield, veterans' care and th industrial point of view. That evening, at 8:00, D William Dock, of Brooklyn, New York, will delive the Shattuck Lecture, his title being "Clinica Significance of Circulatory Peculiarities of Some o the Vital Organs."

The third general session will open at 9:00 a.m on May 21. The program lists seven papers o timely topics of general interest, such as infectiou diarrhea of the newborn and the uses and abuses o chemotherapy. Four section meetings and lunch eons are scheduled for the noon hour, and the fourth general session, which begins at 2:00 p.m. will com prise a symposium on bronchiectasis, consisting o five papers presenting the views of the pathologist roentgenologist, internist, anesthetist and surgeon A cocktail party will be held from 5:00 to 7:00, fol lowed by the annual dinner, at which the gues speaker will be Dr. Harrison H. Shoulders, presiden of the American Medical Association.

The fifth and sixth general sessions will begin a 9:00 a.m. and 2:00 p.m., respectively, on May 22 Fourteen talks on a miscellaneous group of topic are scheduled, and at noon four section meeting and luncheons will be held.

Although it has been necessary to eliminate th continuous motion-picture program and to cut dow on the scientific exhibit owing to lack of space, th technical exhibit will be approximately as large a in previous years. Improvements in diagnostic aid and new therapeutic agents continue to appear a an amazingly rapid rate, and the technical exhibi offers an excellent opportunity for those who attend the meeting to become up to date.

The program for the wives of members includes a reception and tea at the Women's City Club Boston, on the afternoon of May 20 and luncheon at The Country Club, Brookline, on the following day.

The annual golf tournament of the Society will be held at the Woodland Golf Club, Newton, on the afternoon of May 20.

Once again the Committee on Arrangements — Sidney C. Wiggin, chairman, G. Guy Bailey, Harold G. Giddings, Robert L. Goodale and John F. Conlin — deserves praise for devising a program that should have great appeal to the members of the Society. All who can make the necessary arrangements should plan to attend!

THE FULMINANT FORM OF EPIDEMIC HEPATITIS

Lucke and Mallory[1] have recently described the clinical and anatomic findings in a group of fatal cases of acute epidemic hepatitis that may represent an entirely new form of this disease, which they termed "fulminant." Epidemic hepatitis attained pandemic proportions during the war; it occurred in many parts of the world and probably in the armies of most, if not all, of the belligerent nations. In 1944 Lucké[2] described the pathology of this disease in 125 cases that were observed in the Army of the United States in 1942. During the period between August, 1943, and April, 1945, another series, consisting of 196 fatal cases, was accumulated at the Army Institute of Pathology. More than half the latter cases were of the acute form and were of intense severity, terminating fatally in less than ten days. By contrast, not a single equally fulminant case was encountered in the previous series, and this type of case has rarely been noted in other epidemics that have been reported. The usual duration of the fatal disease in Lucké's first series was from four to six weeks: in other words, the course of the fatal hepatitis was predominantly subacute.

This divergence in the duration of the fatal illness reflects the striking difference in the pertinent pathologic changes. Thus, in the fulminant form, the parenchyma of the liver is destroyed completely and uniformly, and this destructive process is accompanied by an intense inflammatory reaction. In the subacute form and in a quarter of the second series of cases, the destruction of the liver was incomplete, the involvement was characteristically not uniform, regenerative hyperplasia of the surviving parenchyma led to the production of much new liver tissue and the inflammation was less pronounced.

The epidemiology of the cases also differed significantly. Most of the cases of hepatitis that occurred in 1942 followed the administration of yellow-fever vaccine containing human serum. In the more recent series such vaccination had not been used, but nearly half the patients had sustained combat injuries. Since most of the seriously wounded patients customarily received transfusions of whole blood, serum or plasma, it can be assumed that a high proportion of the wounded in the latter series were treated in this manner. It was not known, however, in how many cases the causal agent of hepatitis was introduced by therapeutic procedures, especially since large epidemics of hepatitis were prevalent in several of the theaters of war. The assumption that the cases among the wounded were examples of so-called "homologous serum hepatitis" seems justified largely by the relatively long interval between the time of the wound, and presumably of the first transfusion, and the time of onset of the clinical manifestation of the disease. About half the cases, which occurred in nonwounded persons, represented both the epidemic and the endemic variants of naturally occurring hepatitis. Lucké and Mallory's study is largely based on 94 fulminant cases in which the clinical duration did not exceed nine days, but they also studied 39 additional cases that had a duration of from ten to nineteen days.

On the basis of epidemiology, 29 of the cases were classed as endemic and 72 as epidemic variants of spontaneous hepatitis, and 77 cases were presumed to be homologous serum hepatitis following trauma and transfusions of blood or blood derivatives. A careful analysis showed that the epidemiologic type did not in any way determine either the clinical form or the pathological picture of the hepatitis, or whether the case was fulminant or subacute. There was no information whether the mortality rates were the same or different in the epidemiologic variants. The average mortality during the period covered by the study was 0.3 per cent. Serum hepatitis, however, tended to run a considerably shorter course than the naturally occurring disease.

Clinically, the fulminant form of hepatitis was characterized by its abrupt onset and by its severity. It was usually ushered in by one of two syndromes: an "infectious type," in which the disease began with fever, chilliness, shaking chills, malaise, generalized aching and pains in the joints, back and eyes, with gastrointestinal symptoms usually following in a day or so but rarely dominating the picture, or a "gastrointestinal type," with anorexia, nausea and epigastric discomfort as the presenting symptoms. These two types were about equally frequent and often occurred side by side during various epidemics. In the fulminant cases, the initial symptoms sometimes merged with those of the terminal stage, but the subsequent clinical manifestations bore no relation to the prodromal symptoms.

The temperature ranged from 95 to 104°F., with an average of 102°, and usually declined with the onset of jaundice. There was generally a terminal sharp rise in temperature coincident with the onset of profound cerebral disturbances. In contrast to the deep jaundice commonly observed in the subacute form, the jaundice in fulminant hepatitis was often mild, and several anicteric cases were observed. Moderate degrees of nitrogen retention and lowered blood sugar levels were among the noteworthy laboratory findings.

The pathologic lesions, other than those in the liver, were relatively slight. As previously mentioned, the changes in the liver were characterized by an extreme and often complete destruction of the hepatic cells and a marked inflammatory reaction, the involvement usually being uniform throughout the liver. The gross appearance gave no indication either of the extent of parenchymatous destruction or of the degree of inflammatory infiltration. The organ was usually flaccid and moderately shrunken, and the capsule was smooth or finely wrinkled. The cut surface generally presented an exaggerated "nutmeg" pattern, although sometimes it resembled that of an acutely congested spleen. Microscopically, the destructive process was limited to the liver cells. Practically all the parenchymal cells were necrotic and had undergone lysis, and the resultant debris had already been removed at the time of death. The inflammatory cells consisted of mononuclear forms—reticuloendothelial derivatives, plasma cells and lymphocytes. Regenerative hyperplasia of the parenchyma was minimal and was confined to the biliary rather than to the hepatic epithelium. In most cases the pathologic changes in the liver were obviously older than the clinical history suggested, but sometimes the reverse was true.

The kidneys in the majority of cases were the site of fat storage, especially within the cells of the proximal convoluted tubules. There were no significant degenerative changes, and the findings were considered to be the result of the sudden liberation of large amounts of fat from the destroyed liver cells. There was no correlation between the degree of fat storage and the nitrogen retention. The so-called "hepatorenal syndrome," as usually defined, was not observed. Although marked nervous disturbances were noted clinically in the terminal stages, the histologic changes in the brain were usually slight, consisting of a mild and nonspecific encephalopathy. Ascites was present in approximately a fourth of the cases of fulminant hepatitis, and its production was thought to be the result of acute venous stasis in the liver. The incidence of ascites and its extent, however, seemed to be directly proportional to the duration of the disease and were not related to the weight of the liver.

The factors responsible for the appearance of this fulminant form of hepatitis were difficult to assess. It was suggested that a number of more or less interrelated host factors, such as fatigue, trauma and nutritional disturbances, played a dominant role, rather than any specific property of the strain or the amount of the infectious agent.

References

1. Lucké, B., and Mallory, T. Fulminant form of epidemic hepatitis. *Am. J. Path.* 22:867-945, 1946.
2. Lucké, B. Pathology of fatal epidemic hepatitis. *Am. J. Path.* 20: 471-527, 1944.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW DIRECTOR

Nicholas J. Fiumara, M.D., health officer of the Berkshire District of the State Department of Public Health, has been promoted to director of the Division of Venereal Diseases, pending qualification by the Division of Civil Service.

Dr. Fiumara succeeds Dr. George E. Perkins, of Belmont, who died suddenly from injuries sustained in an automobile accident.

A former lieutenant in the Navy Medical Reserve Corps, Dr. Fiumara served with the Navy from June, 1943, to July, 1946. He held the successive posts of medical officer aboard the *U.S.S. Monomoy*, venereal-disease control officer in the Caribbean Theater and commanding officer of Epidemiology Unit 22, which saw service on the West Coast.

Since his detachment from the Navy last year, Dr. Fiumara has been attending the Harvard School of Public Health, from which it is expected he will receive the degree of Master of Public Health in June.

He is a member of the Massachusetts Medical Society, American Public Health Association and Massachusetts Public Health Association and a fellow of the American Medical Association.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1947

Résumé

Diseases	March 1947	March 1946	Seven-Year Median
Chancroid	3	1	2*
Chicken pox	3064	1391	1471
Diphtheria	72	19	16
Dog bite	796	988	733
Dysentery, bacillary	9	14	4
German measles	112	680	316
Gonorrhea	295	424	327
Granuloma inguinale	0	1	1*
Lymphogranuloma venereum	0	2	2*
Malaria	8	63	2
Measles	1794	3081	3126
Meningitis, meningococcal	3	12	21
Meningitis, Pfeiffer-bacillus	3	4	3
Meningitis, pneumococcal	1	5	5†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	0	1†
Meningitis, other forms	1	1	1†
Meningitis, undetermined	9	2	4†
Mumps	1178	831	1349
Pneumonia, lobar	172	243	372
Poliomyelitis	2	2	1
Salmonellosis	15	8	8
Scarlet fever	570	892	1457
Syphilis	364	482	479
Tuberculosis, pulmonary	175	248	248
Tuberculosis, other forms	14	23	20
Typhoid fever	1	3	2
Undulant fever	7	5	5
Whooping cough	645	592	853

*Three-year median.
†Five-year median.

Comment

Diphtheria once again was the leading disease of the month. The number of cases reported has essentially the same ratio to those of 1946 and the seven-year median as that reported in February; however, the number of cases shows an increase of 18 cases over the number of cases reported in February.

Chicken pox was still increased as compared with the number of cases reported in March, 1946, but the excess was not so marked, being approximately three times the number of cases reported in March, 1946, and three times the seven-year median.

Measles and German measles both showed a marked drop compared to the number of cases reported in March, 1946, and to the seven-year median, German measles, in particular, being approximately one sixth the number of cases reported in March, 1946, and one third the seven-year median.

Diseases above the seven-year median were dog bite, bacillary dysentery, poliomyelitis, salmonellosis and undulant fever.

Scarlet fever is at the lowest level since 1918.

Below the seven-year median are gonorrhea, meningitis, lobar pneumonia, syphilis, typhoid fever and whooping cough.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Abington, 1; Belmont, 1; Boston, 30; Cambridge, 1; Chelsea, 3; Chicopee, 5; Easthampton, 2; Everett, 1; Lowell, 1; Lynn, 1; Medford, 1; New Bedford, 4; Newbury, 1; Newton, 1; Norton, 1; Peabody, 1; Reading, 2; Revere, 5; Saugus, 1; Somerville, 3; Southwick, 1; Wellesley, 1; West Newbury, 1; West Springfield, 1; Winchester, 1; Winthrop, 1; total, 72.

Dysentery, amebic, was reported from: Boston, 1; Cambridge, 1; Quincy, 1; total, 3.

Dysentery, bacillary, was reported from: Melrose, 3; Worcester (State Hospital), 6; total, 9.

Encephalitis, infectious, was reported from: Middleboro, 1; New Bedford, 1; total, 2.

Hookworm was reported from: Lowell, 1; total, 1.

Lymphocytic choriomeningitis was reported from: Weymouth, 1; total, 1.

Malaria was reported from: Acton, 1; Boston, 1; Lowell, 1; Lynn, 2; Medford, 2; Worcester, 1; total, 8.

Meningitis, meningococcal, was reported from: Boston, 1; Middleboro, 1; Swampscott, 1; total, 3.

Meningitis, Pfeiffer-bacillus, was reported from: Boston, 1; Brockton, 1; Revere, 1; total, 3.

Meningitis, pneumococcal, was reported from: Boston, 1; total, 1.

Meningitis, other forms, was reported from: Mansfield, 1; total, 1.

Meningitis, undetermined, was reported from: Cambridge, 3; Fall River, 1; Milton, 1; Newton, 1; Salem, 1; Williamstown, 1; Worcester, 1; total, 9.

Poliomyelitis was reported from: Chicopee, 1; Lynn, 1; total, 2.

Salmonellosis was reported from: Belmont, 1; Boston, 2; Gardner, 1; Holyoke, 1; Melrose, 1; Peabody, 2; Quincy, 1; Salem, 1; Somerville, 1; Southbridge, 2; Springfield, 1; Sutton, 1; total, 15.

Septic sore throat was reported from: Boston, 5; Bourne, 1; East Bridgewater, 1; Grafton, 1; Holyoke, 1; Malden, 1; Merrimac, 1; Newburyport, 1; West Newbury, 2; total, 14.

Tetanus was reported from: Weymouth, 1; total, 1.

Trachoma was reported from: Boston, 1; Cummington, 1; total, 2.

Trichinosis was reported from: Boston, 5; Malden, 1; Middleboro, 1; Wenham, 2; total, 9.

Tularemia was reported from: Grafton, 1; total, 1.

Typhoid fever was reported from: New Bedford, 1; total, 1.

Undulant fever was reported from: Adams, 1; Amesbury, 1; Auburn, 1; Dartmouth, 1; Holyoke, 1; Springfield, 1; Worcester, 1; total, 7.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Gardner (Worcester subclinic)	May 13	John W. O'Meara
Worcester	May 16	John W. O'Meara
Springfield	May 20	Garry deN. Hough, Jr.
Pittsfield	May 21	Frank A. Slowick
Fall River	May 26	David S. Grice
Hyannis	May 29	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

OFFICERS OF THE MASSACHUSETTS MEDICAL SOCIETY, 1946-1947

Blackstone

DR. EDWARD P. BAGG, *President-Elect*

PROGRAM OF THE ONE HUNDRED AND SIXTY-SIXTH ANNIVERSARY OF THE MASSACHUSETTS MEDICAL SOCIETY

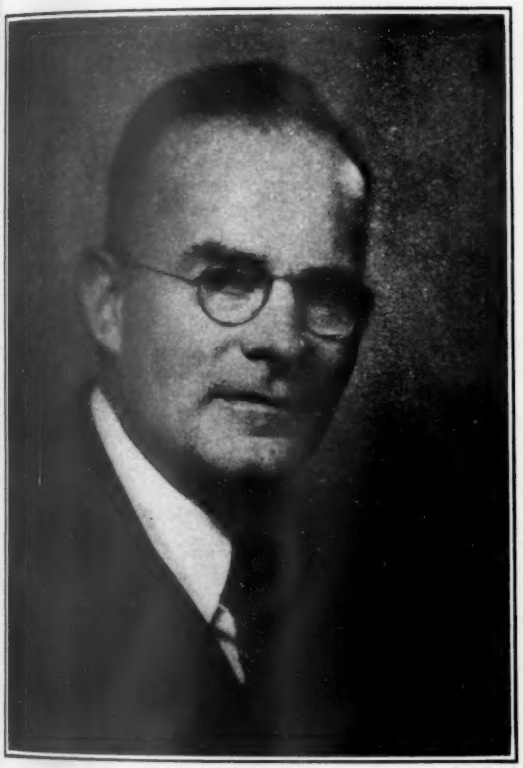
Monday, Tuesday, Wednesday and Thursday, May 19, 20, 21 and 22, Hotel Statler, Boston

The Registration Desk will be located on the Mezzanine Floor, and all who attend the meeting are requested to register.

MONDAY AFTERNOON, MAY 19

4:30 **Supervising Censors' Meeting** (PARLOR C).

6:00 **Cotting Supper for Councilors** (PARLORS A AND B).



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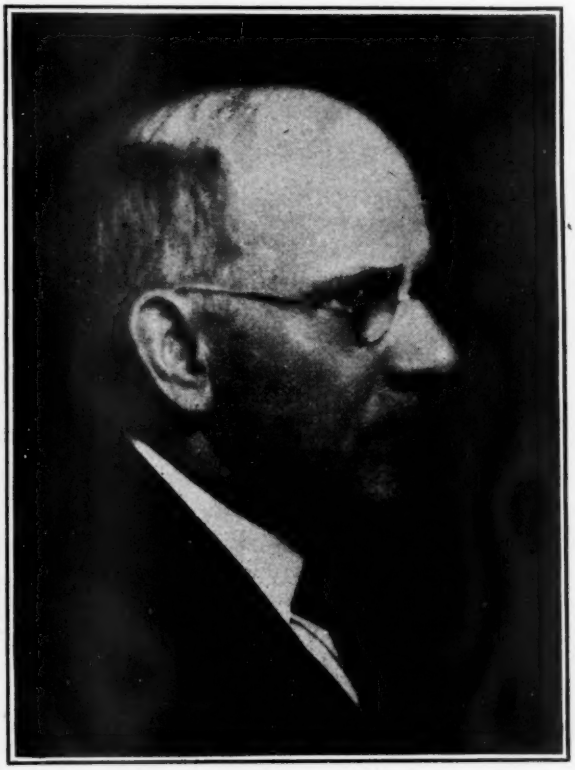

DR. ISAAC S. F. DODD, *Vice-President*

MONDAY EVENING, MAY 19

7:00 **Annual Meeting of the Council** (GEORGIAN ROOM).

TUESDAY MORNING, MAY 20

First General Session

GEORGIAN ROOM

DR. DANIEL L. LYNCH, *Chairman*
DR. GERALD L. DOHERTY, *Co-chairman*

Symposium on Industrial Medicine

9:05 *Toxic Effects of Gases and Vapors.* DR. MARSHALL CLINTON, Boston. Associate in industrial hygiene, Harvard School of Public Health. With a discussion by DR. HARRIET L. HARDY, Boston. Physician, Division of Occupational Hygiene, Commonwealth of Massachusetts.

9:30 *The Control of Respiratory Infections in Industry.* DR. GEORGE F. WILKINS, Boston. Assistant medical director, New England Telephone and Telegraph Company. With a discussion by DR. ARLIE BOCK, Boston. Professor of hygiene, Harvard University.

9:55 *Rehabilitation of the Employee Injured in Industry.* DR. ALEXANDER P. AITKEN, Boston. Medical director, Rehabilitation Center, Liberty Mutual Insurance Company, Boston. With a discussion by DR. AUGUSTUS THORNDIKE, JR., Boston. Chief surgeon, Department of Hygiene, Harvard University.

10:20 *Occupational Dermatoses.* DR. JOHN G. DOWNING, Boston. Professor of dermatology, Tufts College Medical School and Boston University School of Medicine.

11:00 **Annual Meeting of the Massachusetts Medical Society** (Georgian Room).

Annual Oration (following annual meeting): Medical Care in Our Free Society. Dr. Leland S. McKittrick, Boston. Surgeon-in-chief, Palmer Memorial Hospital; visiting surgeon, Massachusetts General Hospital.

Annual Luncheon (Parlors A, B and C): tickets must be procured in advance of the meeting.

TUESDAY AFTERNOON, MAY 20

Second General Session

Georgian Room

Dr. Reginald Fitz, *Chairman*
Dr. Albert A. Hornor, *Co-chairman*

Symposium: The Distribution of Medical Care for the People of Massachusetts

2:00 *Principles of the Massachusetts Medical Society.* Dr. Elmer S. Bagnall, Groveland. Past-president, Massachusetts Medical Society.

2:25 *The Contribution of the Blue Cross.* Mr. Reginald F. Cahalane, Boston. Executive director, Massachusetts Hospital Service, Inc., and Massachusetts Medical Service, Inc.; vice-chairman, Blue Cross Commission.

2:50 *The Contribution of the Blue Shield.* Dr. Charles G. Hayden, Boston. Medical director, Massachusetts Hospital Service, Inc., and Massachusetts Medical Service, Inc.; member of the Commission, Associated Medical Care Plans.

3:15 *Medical and Hospital Care of the Veterans in Massachusetts.* Dr. Winthrop Adams, Boston. Branch medical director, Veterans Administration, Boston.

3:40 *What Industry Thinks About the Program.* Mr. Jarvis Hunt, North Attleboro. General counsel, Associated Industries of Massachusetts; former president, Massachusetts State Senate.

4:05 *Question-and-Answer Period.*

TUESDAY EVENING, MAY 20

Georgian Room

8:00 **The Shattuck Lecture.** Clinical Significance of Circulatory Peculiarities of Some of the Vital Organs. Dr. William Dock, Brooklyn, New York. Professor of medicine, Long Island College of Medicine; director of medical service, College Division, King's County Hospital.

WEDNESDAY MORNING, MAY 21

Third General Session

Georgian Room

Dr. Isaac S. F. Dodd, *Chairman*
Dr. Allen Rice, *Co-chairman*

9:00 *The Advantages of the Extraperitoneal Cesarean Section.* Dr. Roy J. Heffernan, Brookline. Visiting obstetrician and gynecologist, Carney Hospital; consulting obstetrician and gynecologist, Faul[kner] and St. Margaret's hospitals.

9:25 *Diarrhea of the Newborn: Its cause and preventio[n].* Dr. Stewart H. Clifford, Boston. Visiti[ng] pediatrician, Boston Lying-in Hospital; visi[ting] ing physician, Infants' and Children's Hospit[al]; instructor in pediatrics and child hygie[ne], Harvard Medical School.

9:50 *Management of Diabetes and Its Complications.* D[r.] Priscilla White, Boston. Physician, N[ew] England Deaconess Hospital.

10:15 *Cytologic Diagnosis of Carcinoma of Various Orga[ns] of the Body.* Dr. Joe V. Meigs, Boston. Chi[ef] Vincent Memorial Hospital, Massachuse[tts] General Hospital; clinical professor of gyneco[l]ogy, Harvard Medical School. Dr. Maur[ice] Fremont-Smith, Boston. Associate physici[an] Massachusetts General Hospital; instructor [in] medicine, Harvard Medical School.

10:40 *Ramifications of the Xanthomas.* Dr. Fred D. Wei[l]man, Philadelphia. Professor of research [in] dermatology and mycology, University of Penn[sylvania] sylvania School of Medicine.

11:05 *A Review of Some Recently Defined Virus Diseas[es].* Dr. John F. Enders, Boston. Director of re[search], search, Department of Infectious Disease[s], Children's Hospital; associate professor of bac[teriology] teriology and immunology, Harvard Medic[al] School.

11:30 *The Uses and Abuses of Chemotherapy.* Dr. Perri[n] H. Long, Baltimore. Professor of preventive medicine, Johns Hopkins University School o[f] Medicine.

WEDNESDAY NOON, MAY 21

Section Meetings and Luncheons

12:00 M. — 2:00 P. M.

Section of Medicine

Parlor A

Dr. Francis C. Hall, Boston, *Vice-chairman*
Dr. Laurence B. Ellis, Boston, *Secretary*

Modern Concepts of Host-Parasite Relations in Infectious Diseases. Dr. Perrin H. Long, Baltimore.

Section of Pediatrics

Parlor B

Dr. Hyman Green, Boston, *Chairman*
Dr. Gerald N. Hoeffel, Boston, *Secretary*

Virus Diseases and the Pediatrician. Dr. Charles A. Janeway, Boston. Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School; physician-in-chief, Infants' and Children's Hospital.

Section of Dermatology and Syphilology

Parlor C

Dr. Jacob Swartz, Brookline, *Chairman*
Dr. Francis Thurmon, Boston, *Secretary*

Problems in Mycological Technic. Dr. Frederick D. Weidman, Philadelphia. Professor in dermatologic and mycologic research, University of Pennsylvania School of Medicine.

Section of Physiotherapy

Hancock Room

Dr. William D. McFee, Haverhill, *Chairman*
Dr. Henry A. Tadgell, Belchertown, *Secretary*

Reconditioning of the Arm Amputee. Dr. Augustus Thorndike, Jr., Boston.

A Sound Motion Picture Entitled "The Diary of a Sergeant."

WEDNESDAY AFTERNOON, MAY 21

Fourth General Session

Georgian Room

Dr. Richard H. Sweet, *Chairman*
Dr. Louis H. Nason, *Co-chairman*

Symposium on Bronchiectasis

2:00 *The Pathologist Pursues the Cause.* Dr. Tracy B. Mallory, Boston. Director, Department of Pathology and Bacteriology, Massachusetts General Hospital.

2:25 *The Roentgenologist Makes the Diagnosis.* Dr. Hugh F. Hare, Boston. Director, Department of Radiology, Lahey Clinic.

2:50 *The Physician Thinks about Treatment and Prevention.* Dr. Theodore L. Badger, Boston. Consultant on disease of the lungs, Veterans Administration; instructor in medicine, Harvard Medical School.

3:15 *The Role of Anesthesia.* Dr. Lloyd H. Mousel, Washington, D. C. Consultant to the Surgeon General, United States Army; branch section chief, Department of Anesthesiology, George Washington University School of Medicine.

3:40 *The Contribution of the Thoracic Surgeon.* Dr. John W. Strieder, Brookline. Surgeon-in-chief for thoracic surgery, Boston City Hospital and Massachusetts Memorial Hospitals; assistant professor of thoracic surgery, Boston University School of Medicine.

4:05 *Question-and-Answer Period.*

WEDNESDAY EVENING, MAY 21

5:00 **Cocktail Party** (Salle Moderne)
Tickets must be procured in advance.

7:00 **Annual Dinner of the Massachusetts Medical Society** (Georgian Room).

Presiding:

Dr. Dwight O'Hara, president, Massachusetts Medical Society.

Guest Speaker

Dr. Harrison H. Shoulders, president, American Medical Association. The Responsibilities of the Medical Profession.

Ladies may be invited to attend the dinner.

Tickets for the dinner *must* be procured in advance of the meeting.

THURSDAY MORNING, MAY 22

Fifth General Session

Georgian Room

Dr. Franklin G. Balch, Jr., *Chairman*
Dr. Walter E. Garrey, *Co-chairman*

9:00 *Operating-Room Technic.* Dr. Carl W. Walter, Boston. Senior associate in surgery, Peter Bent Brigham Hospital; assistant professor of surgery, Harvard Medical School.

9:25 *Fenestration Operation for Otosclerosis.* Dr. Philip E. Meltzer, Boston. Surgeon, Massachusetts Eye and Ear Infirmary; professor of otolaryngology, Tufts College Medical School.

9:50 *Thiouracil and Allied Drugs in Hyperthyroidism.* Dr. Elmer C. Bartels, Boston. Member, Department of Internal Medicine, Lahey Clinic; staff member, New England Deaconess and New England Baptist hospitals.

10:15 *The Disabled Veteran of World War II: An analysis of 600 cases examined at Harvard University.* Dr. Augustus Thorndike, Jr., Boston.

10:40 *The Use of Anesthetic Drugs in Medical Practice.* Dr. Perry P. Volpitto, Augusta, Georgia. Professor of anesthesiology, University of Georgia School of Medicine.

11:05 *Surgical Treatment of Congenital Heart Disease.* Dr. Robert E. Gross, Boston. Surgeon-in-chief, Children's Hospital.

11:30 *A Motion Picture Entitled "Foreign Bodies in the Heart."* With a discussion by Dr. Dwight E. Harken, Brookline. Visiting surgeon in thoracic surgery, Boston City and Cambridge hospitals; instructor in surgery, Tufts College Medical School.

THURSDAY NOON, MAY 22

Section Meetings and Luncheons

12:00 M. — 2:00 P.M.

Section of Surgery

Salle Moderne

Dr. Alexander A. J. Campbell, Boston, *Chairman*
Dr. George S. Reynolds, Pittsfield, *Secretary*

Venous Thrombosis. Dr. Michael E. DeBakey, New Orleans. Associate professor of surgery, Tulane University of Louisiana School of Medicine.

Section of Obstetrics and Gynecology

Parlor A

Dr. William J. McDonald, Boston, *Chairman*
Dr. Arthur T. Hertig, Boston, *Vice-chairman*
Dr. George Van S. Smith, Brookline, *Secretary*

The Treatment of Vaginal Discharge. Dr. Christopher J. Duncan, Brookline. Visiting Surgeon, Free Hospital for Women, Brookline; assistant obstetrician, Massachusetts General Hospital and Boston City Hospital.

Section of Radiology

PARLOR C

DR. EDWARD B. D. NEUHAUSER, Cambridge, *Chairman*
DR. HUGH F. HARE, Boston, *Secretary*

The Roentgenologist and the Orthopedic Surgeon. DR. DAVID S. GRICE, Boston. Junior associate in orthopedic surgery, Children's Hospital and Peter Bent Brigham Hospital; assistant in orthopedics, Harvard Medical School.

Section of Anesthesiology

PARLOR B

DR. SIDNEY C. WIGGIN, Waban, *Chairman*
DR. MORRIS J. NICHOLSON, Boston, *Secretary*

Standardization of the Economics of Anesthesia. DR. PERRY P. VOLPITTO, Augusta, Georgia.

THURSDAY AFTERNOON, MAY 22

Sixth General Session

GEORGIAN ROOM

DR. HOWARD F. ROOT, *Chairman*
DR. GORDON M. MORRISON, *Co-chairman*

2:00 *Anticoagulation Treatment of Postoperative Venous Thrombosis and Pulmonary Embolism.* DR. JAMES A. EVANS, Boston. Physician, Lahey Clinic; physician, New England Baptist and New England Deaconess hospitals.

2:25 *Thrombophlebitis and Phlebothrombosis.* DR. MICHAEL E. DEBAKEY, New Orleans.

2:50 *The Practical Importance of Modern Concepts of Psychosomatic Relations.* DR. ALFRED O. LUDWIG, Boston. Assistant psychiatrist, Massachusetts General Hospital; staff psychiatrist, Robert Breck Brigham Hospital; consultant, Office of the Surgeon-General, Veterans Administration.

3:15 *The Clinical Effectiveness of Transthoracic Vagus Resection in the Treatment of Peptic Ulcer.* DR. FRANCIS D. MOORE, Boston. Assistant in surgery, Massachusetts General Hospital; associate in surgery, Harvard Medical School.

3:40 *The Services Offered to the Physician by the Massachusetts Department of Public Health.* DR. VLADO A. GETTING, Boston. Commissioner, Department of Public Health, Commonwealth of Massachusetts.

4:05 *The Present-Day Status of Poliomyelitis.* DR. WILLIAM T. GREEN, Boston. Chief, Orthopedic Service, Children's Hospital; clinical professor of orthopedic surgery, Harvard Medical School.

4:30 *Recent Trends and Treatment in Allergy.* DR. WALTER S. BURRAGE, Boston. Assistant physician, Massachusetts General Hospital; allergist, Newton-Wellesley Hospital; chief of allergy, Branch No. 1, Veterans Administration.

TECHNICAL EXHIBITS

	BOOTH NO.
Abbott Laboratories	56
Alkalol Company	22
Ames Company, Inc.	44
Ayerst, McKenna & Harrison, Ltd.	19
Ba-Bee Dietary Service, Inc.	96
Chester Baker, Inc.	54
Baker Laboratories	61
Bard-Parker Company, Inc.	78
Best Foods, Inc.	76
Bilhuber-Knoll Corp.	34
The Borden Company	28
Boston Medical Supply Company	85
Brewer & Company, Inc.	3 & 4
Bristol Laboratories, Inc.	75
Buffington's, Inc.	39
Burroughs Wellcome & Company	23
Cambridge Instrument Company, Inc.	80
Camel Cigarettes	11 & 12
Certified Milk Producers Association	60
Ciba Pharmaceutical Products, Inc.	67
Coca-Cola Bottling Company	13 & 14
Crosbie-Macdonald Company	46
Davies, Rose & Company, Ltd.	40
Denver Chemical Company	74
Doho Chemical Corp.	25
Dy-Dee Service, Inc.	70
Eaton Laboratories, Inc.	Stage
J. H. Emerson Company	9
C. B. Fleet & Company	45
General Electric X-Ray Corporation	58 & 59
Gerber Products Company	43
J. E. Hanger, Inc.	35
Hanovia Chemical & Mfg. Company	51
Harper-Wallins Corporation	10
Harper X-Ray Corporation	62
H. J. Heinz Company	27
Hoffmann-La Roche, Inc.	29
Hygeia Nursing Bottle Company	82
The Kelley-Koett Mfg. Company	7
Kellogg Company	89
Kidde Manufacturing Co., Inc.	77
Laben, George	32
Lederle Laboratories, Inc.	57
Libby, McNeill & Libby	20
The Liebel-Flarsheim Company	64
Eli Lilly & Company	38
J. B. Lippincott Company	68
M & R Dietetic Laboratories	16
E. F. Mahady Company	Stage
McIntosh Electrical Corporation	63
McNeil Laboratories	8A
Mead, Johnson & Company	52 & 53
Medical Clearing Bureau, Inc.	92
Medical Protective Company	21
Mellin's Food Company	31
The Mennen Company	65
William S. Merrell Company	69
National Dairy Products Company	66
The National Drug Company	5
Nestle's Milk Products, Inc.	83
T. J. Noonan Company	79
Parke, Davis & Company	72
E. L. Patch Company	15

Pet Milk Sales Corporation ..... 86 & 87
Philip Morris & Co., Ltd., Inc. 49
Pitman-Moore Company 84
Professional Equipment & Hospital Supply Co. 93
Rare Chemicals, Incorporated 81
L. & B. Reiner 33
Sanborn Company 71
Sandoz Chemical Works, Inc. 42
Schering Corporation 41
G. D. Searle & Company 24
Sharp & Dohme, Inc. 50
Smith, Kline & French Laboratories 8
Spencer, Inc. 17
E. R. Squibb & Sons 73
Frederick Stearns & Company ..... 47 & 48
Surgeons & Physicians Supply Company 30
Swift & Company 91
Tailby-Nason Company 17
U. S. Vitamin Corporation 95
Vaponefrin Company 6
Walker Vitamin Products, Inc. 90
Westinghouse Electric Corporation ..... 1 & 2
White Laboratories, Inc. ..... 36 & 37
Winthrop Chemical Co., Inc. 55
Wyeth, Incorporated 88
F. E. Young & Company 26

CORRESPONDENCE

DIGITALIS

To the Editor: Another excellent article on medical progress, namely, "Digitalis," by Drs. Freedberg and Zoll, appeared in the December 6, 1946, issue of the *Journal*. A paragraph deserves emphasis as an example of the unsatisfactory state of our knowledge concerning one of our most extensively studied and generally used drugs. It states:

> One cat unit is defined as the amount of digitalis per kilogram of cat weight that produces a lethal effect under certain defined conditions. One *U.S.P. XII* unit of digitalis represents the same potency as 0.1 gm. of the *U.S.P.* digitalis reference standard powder, when assayed as directed. The digitalis leaves from which the reference powder was made, however, were of high potency, so that 1 *U.S.P. XII* unit is equivalent to 20 per cent more than 1 cat unit. It is particularly important for the physician to know the digitalis preparation he is using, since the clinical effect of digitalis, standardized according to *U.S.P. XII*, is approximately 25 per cent weaker than *U.S.P. XI*, which in turn is approximately 50 per cent stronger than *U.S.P. X*.

In reading the article one also learns that the cat method of assay measures the lethal potency of digitalis and not specific therapeutic action; also that by comparative assays in cats and human beings, a group of digitalis preparations with the same strength in cat units showed a tenfold range in potency in human subjects.

This, obviously, is hardly a satisfactory standardization of a therapeutic agent. Perhaps it is somewhat natural, therefore, for those of us who are not cardiologists to ask why one continues to perplex physicians with cat units and complicated discussions of digitalis therapy when a crystallized digitaline has been available since 1866 that is a thousand times as therapeutically effective as digitalis leaf and has certain other advantages. Quoting again from the same progress article:

> In summary, the advantages of digitoxin are that it is a pure chemical that is stable and does not require bioassay and that it is completely absorbed from the gastrointestinal tract, so that oral and intravenous doses are the same and interchangeable. Furthermore, the small amount of digitoxin necessary for digitalization permits administration of a large fraction in a single dose, with only a small incidence of local gastrointestinal irritation. The rapid onset of action makes for quick digitalization by the oral route so that intravenous administration is rarely necessary. The prolonged duration of action, like that of whole-leaf digitalis, makes for easy maintenance. It is thus the drug of choice when a purified preparation is desired.

Is it naïveté or common sense that also leads the noncardiologist to ask when a purified preparation is not desirable?

If the answer is one of expense, this could be overcome by an increased demand by physicians for the pure product. If it is because of conservative reverence for a time-tested therapeutic agent, the seventy years of digitoxin would appear to remove that product from the classification of *nouveaux*.

ALLAN M. BUTLER, M.D.
Massachusetts General Hospital
Boston

UNLAWFUL IMPORTATION OF NARCOTIC DRUGS

To the Editor: From time to time the Bureau of Narcotics and the Bureau of Customs have received complaints from physicians when narcotic drugs have been seized from their medical bags at the time of re-entering the United States from a visit to Mexico or Canada.

In view of the above fact, the Commissioner of Narcotics has requested the following notice be printed in medical journals of states close to either Canada or Mexico.

> Under the provisions of the Narcotic Drugs Import and Export Act, it is unlawful for a physician to carry narcotic drugs in his medical bag back and forth between the United States and Mexico and between the United States and Canada. Narcotic drugs found in the possession of a physician on returning to the United States are seized and forfeited. Because of lack of knowledge of the law, many physicians are caused embarrassment and inconvenience when traveling between this country and Mexico or Canada. This information is published in order that physicians may be correctly informed with reference to this provision of the federal law.

P. A. WILLIAMS
District Supervisor

District Office
Bureau of Narcotics
P. O. Box 2138
Boston 6

BOOK REVIEWS

Public Health and Welfare Reorganization: The postwar problem in the Canadian provinces. By Harry M. Cassidy, Ph.D. 8°, cloth, 464 pp. Toronto: Ryerson Press, 1945. Cloth $4.50; paper $3.50.

This work is a sequel to the author's *Social Security and Reconstruction in Canada*, published in 1943. The text is divided into four parts. The first discusses premises for provincial planning, with an analysis of the present system and suggested adjustments in the provincial systems. The second and third are devoted to British Columbia, the Prairie provinces, Ontario, Quebec and the Maritime provinces. The history of public health in these localities, the present status and suggested programs for the future are considered in detail. The fourth part is a summary pointing out the flaws in the present system and outlining the principles of reorganization. The importance of local units and national leadership is stressed.

On the basis of his practical experience and study the author is convinced that there are serious weaknesses in the Canadian provincial and local social services, including the health services. He believes that drastic changes in organization and administration are required before these services can reach high standards.

This document should be in all public-health collections.

Clinical Roentgenology of the Heart. By John B. Schwedel, M.D. *Annals of Roentgenology*, Volume XVIII. 4°, cloth, 380 pp., with 749 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. $12.00.

This volume presents a brief summary of the present status of the roentgenologic study of the heart and great vessels.

There are many illustrations, including not only roentgenograms but also diagrams and photographs of pathological specimens. The text is clear, the pictures are well selected, and the volume is well printed and bound. Of particular interest is the emphasis on normal variations in Chapter 4.

As in any brief work of the sort, some things are too much abbreviated. It would be of value to add illustrations of a dissecting aneurysm of the aorta, both before and after its development. A more typical illustration of constrictive pericarditis is also desirable and, similarly, a roentgenogram of the heart showing auricular septal defect without mitral stenosis. Tricuspid atresia might well have been added as one of the more newly recognizable congenital defects. It should be noted that, on occasion, funnel chest may compress as well as displace the heart and thus embarrass the circulation.

The electrocardiogram reproduced in Figure 53*J* on page 90 is upside down, as is that in Figure 72*C* on page 128. In the last sentence of page 319 "left" should read "right."

This book can be recommended as an up-to-date exposition of roentgenology of the heart and great vessels.

It's How You Take It. By G. Colket Caner, M.D. 12°, cloth, 152 pp. New York: Coward-McCann, Incorporated, 1946. $2.00.

Physicians will find this book a practical volume to recommend to patients as an adjunct to psychotherapy. A troubled person can read it without risk and can find in it pertinent discussion of problems closely related to his own, and a healthy person can gain through it understanding that will enable him to function at a higher level of effectiveness and contentment. The book is concise, simple and free from technical language.

The literary device of posing questions, used in the book, stimulates interest and attention. Dr. Caner's answers, which are constructive and replete with wholesome ideas, make clear what a person can do toward helping himself. They give an understanding of psychosomatic reactions and of the effect of various attitudes on relations with others and on emotional stability. The common sense and idealism of the book make it particularly suited to young persons, but it will also appeal to adults, particularly to parents and teachers. The volume could be profitably used in high schools as a basis for the teaching of mental hygiene, whose preventive aspects it covers thoroughly and soundly. It is a book to be studied and to be read thoughtfully over and over again. Used in this way, it will be extremely helpful.

Diseases of the Adrenals. By Louis J. Soffer, M.D. 8°, cloth, 304 pp., with 42 illustrations and 2 colored plates. Philadelphia: Lea and Febiger, 1946. $5.50.

This book is constructed along orthodox lines and covers the adrenal gland from medulla to cortex. One of its most valuable features is an account of methods now in use for determining the concentrations of sodium or potassium in serum and urine and for assaying the excretion of androgens, estrogens and 17-ketosteroids. The part of the monograph that describes Addison's disease and the clinical manifestations of the different tumors that may involve the adrenal glands is well written. The color plates are excellent. On the whole, the volume represents much industry and can be recommended as a useful work of reference.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Mongolism and Cretinism: A study of the clinical manifestations and the general pathology of pituitary and thyroid deficiency. By Clemens E. Benda, M.D., director, Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham, Massachusetts, instructor in neuropathology, Harvard Medical School, and assistant in psychiatry, Massachusetts General Hospital. 8°, cloth, 310 pp., with 103 illustrations and 48 tables. New York: Grune and Stratton, 1946. $6.50.

Dentistry: An agency of health service. By Malcolm W. Carr, D.D.S., director of oral surgery and visiting oral surgeon, Metropolitan Hospital, attending oral surgeon, St. Luke's Hospital, Knickerbocker Hospital, Polyclinic Hospital and Flower and Fifth Avenue Hospitals, consultant oral surgeon, Roosevelt Hospital, and lecturer in oral surgery, Graduate School of Medicine, University of Pennsylvania. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. 8°, cloth, 216 pp. New York: The Commonwealth Fund, 1946. $1.50.

Jerome Carden. By James Eckman. 4°, paper, 120 pp. Baltimore: Johns Hopkins Press, 1946. $2.00.

Eight Years of Public Health Work: Jones County, Mississippi, 1937-1944. By Harry E. Handley, M.D., assistant director, Division of Public Health, The Commonwealth Fund; and Carolina R. Randolph, director of studies, Division of Public Health, The Commonwealth Fund. 12°, paper, 80 pp., with 47 tables. New York: The Commonwealth Fund, 1946. 50 cents.

Modern Development of Chemotherapy. By E. Havinga; H. W. Julius; H. Veldstra; and K. C. Winkler. 8°, paper, 175 pp., with 31 illustrations and 8 tables. New York: Elsevier Publishing Company, Incorporated, 1946. $3.50.

Autopsy Diagnosis and Technic. By Otto Saphir, M.D., pathologist, Michael Reese Hospital, and professor of pathology, University of Illinois Medical School, Chicago. With a foreword by Ludwig Hektoen, M.D. Second edition, revised and enlarged. 12°, cloth, 405 pp., with 69 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. $5.00.

Medicine in Industry. By Bernhard J. Stern, Ph.D., lecturer in sociology, Columbia University, and visiting professor of sociology, Yale University. Studies of the New York Academy of Medicine Committee on Medicine and the Changing Order. 8°, cloth, 209 pp. New York: The Commonwealth Fund, 1946. $1.50.

The Diagnosis and Treatment of Pulmonary Tuberculosis. By Moses J. Stone, M.D., assistant professor in medicine, Boston University School of Medicine, instructor in medicine, Tufts College Medical School, and physician-in-chief, Chest Clinics, Beth Israel and Massachusetts Memorial hospitals; and Paul Dufault, M.D., superintendent, Rutland State Sanatorium, Rutland, Massachusetts. With a foreword by Henry D. Chadwick, M.D. 12°, cloth, 325 pp., with 93 illustrations. Philadelphia: Lea and Febiger, 1946. $3.50.

Mother and Baby Care in Pictures. By Louise Zabriskie, R.N., director, Maternity Consultation Service, New York City, lecturer, New York University, and field director, Maternity Center Association, New York City. Third edition, modernized. 8°, cloth, 203 pp., with 229 illustrations and 7 tables. Philadelphia: J. B. Lippincott Company. $2.00.

Complete Handbook on State Medicine. By J. Weston Walch. 4°, paper, 170 pp. Portland, Maine: J. Weston Walch, 1946. $2.50.

NOTICES

ANNOUNCEMENTS

Dr. Harrison E. Kennard announces the reopening of his office at 374 Marlborough Street, Boston, for the practice of general surgery.

Dr. Robert C. Thompson announces the opening of his office at 293 Humphrey Street, Swampscott, for the practice of general medicine and surgery.

(*Notices continued on page xvii*)

NOTICES (*Continued from page* 728)

AMERICAN HEART ASSOCIATION

The annual meeting of the American Heart Association will be held at the Hotel President, Atlantic City, on June 6–8, 1947, prior to the annual session of the American Medical Association. Members of the medical profession and other interested persons may attend the scientific sessions on June 6 and 7.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, May 15

Friday, May 16

*9:00–10:00 a.m. The Control of Ascitic-Fluid Formation in Hepatic Cirrhosis by Albumin; Mechanisms of Albumin Action in Water and Sodium Balance of Other Diseases. Dr. S. Howard Armstrong. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

Monday, May 19

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

Tuesday, May 20

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

Wednesday, May 21

*9:00–10:00 a.m. Porphyrins. Dr. Marvin Bloom. Joseph H. Pratt Diagnostic Hospital.

*11:00 a.m.–12:00 m. Medical Clinic. Amphitheater, Children's Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

May 17. Reunion at Springfield Hospital. Page 682, issue of May 1.

May 19–22. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

May 20–22. Massachusetts Physicians' Art Association. Page 340, issue of February 27.

June 5–8. American College of Chest Physicians. Page 418, issue of March 13.

June 6–8. American Heart Association. Notice above.

June 7 and 8. American Society for the Study of Sterility. Page 304, issue of February 20.

June 9–13. American Medical Association. Page 698, issue of November 7.

June 11. Harvard Medical Alumni Association. Page 646, issue of April 24.

June 11. Tufts Medical Alumni Dinner. Page 646, issue of April 24.

June 16–18. New England Health Institute. Page 340, issue of February 27.

June 30–July 3. American Urological Association. Hotel Statler, Buffalo.

September 2–6. American Congress of Physical Medicine. Page 610, issue of April 17.

September 2–7. International Cancer Research Congress. Page 340, issue of February 27.

September 8–12. Third American Congress on Obstetrics and Gynecology. Page 340, issue of February 27.

October 6–10. American Public Health Association. Page 456, issue of March 20.

District Medical Society

PLYMOUTH

May 15. Lakeville Sanatorium, Lakeville.

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The Ophthalmological Study Council
BASIC COURSE IN OPHTHALMOLOGY

Westbrook Junior College, Portland, Maine, June 20 to September 13, 1947. All the basic subjects required by the American Board of Ophthalmology. Laboratory work in Pathology and Optics. Practical work in Slit Lamp, Perimetry and Refraction.

Fee: $300; single subjects, $40 a week.

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A. Finesinger, M.D., *Psychiatrist* — C. Saltzman, M.D., *Psychiatrist*

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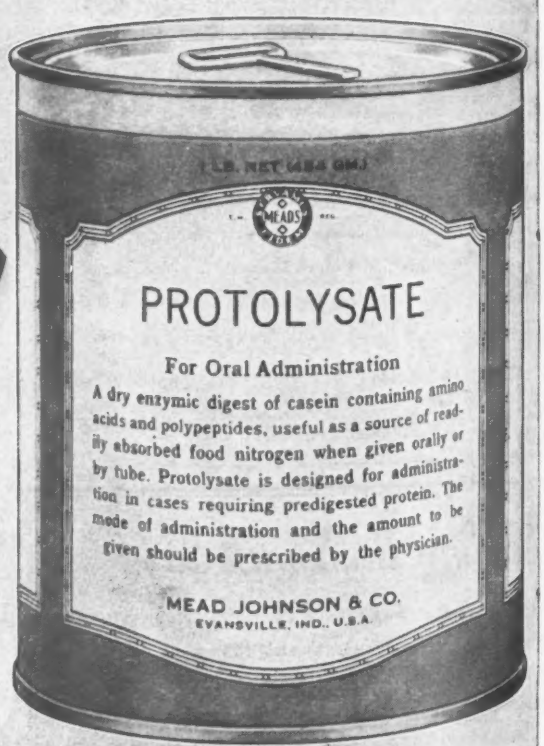
for oral and tube feeding of amino acids

Like Amigen, Protolysate is an enzymic digest of casein and consists of amino acids and polypeptides. Like Amigen, Protolysate supplies the nitrogen essential for maintenance, repair and growth.

Unlike Amigen, which may be employed both orally and parenterally, Protolysate is designed only for oral use.


1 LB. NET (454 GM.)
MEADS
PROTOLYSATE
For Oral Administration
A dry enzymic digest of casein containing amino acids and polypeptides, useful as a source of readily absorbed food nitrogen when given orally or by tube. Protolysate is designed for administration in cases requiring predigested protein. The mode of administration and the amount to be given should be prescribed by the physician.
MEAD JOHNSON & CO.
EVANSVILLE, IND., U.S.A.

1 lb. cans at drug stores

MEAD JOHNSON & CO., EVANSVILLE 21, INDIANA

There is no shortage now of AMIGEN for parenteral use. There is no shortage now of PROTOLYSATE for oral use.